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ACTIVITY IN THE SIMPLEST SPINAL REFLEX PATHWAYS

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(Received for publication May 21, 1940)

ALTHOUGH Cajal (1890, 1894) demonstrated that collaterals of the dorsal root fibers extend through the cord to the anterior horn, there to make synaptic connections with motoneurons, and although reflex arcs of two neurons, *i.e.*, of one synaptic relay, have played a prominent role in schemata of cord activity (*cf.* Cajal, 1909), there has been little physiological evidence of activity in such direct pathways.

Most of the determinations of the central reflex time for homolateral responses in the cord have given minimal values of approximately 3 to 5 msec. (Jolly, 1911; Forbes and Gregg, 1915; Eccles and Sherrington, 1931a). Eccles and Sherrington, however, found that these values, determined by recording the activity of a flexor muscle, may be greatly reduced when the cord is conditioned by a previous volley arriving over the dorsal roots; and Eccles and Pritchard (1937), by applying strong electrical stimuli to dorsal roots, obtained from the unconditioned cord ventral root discharges with reduced latencies of 0.7 to 1.0 msec. Since, according to Lorente de Nó (1935a, c, d; 1938a), the synaptic delay at the motoneurons of the third cranial nucleus varies within the narrow limits of 0.5–0.6 to 0.8–0.9 msec., and since comparable delays have been observed in other pathways (Kemp, Coppée and Robinson, 1937; Bishop and O'Leary, 1938), it is likely, as Eccles (1939) points out, that these minimal central reflex times for the cord pertain to two-neuron pathways.

In the present work determinations of the synaptic delays at neurons in the spinal cord, in conjunction with measurements of central reflex times, demonstrate the validity of this interpretation. Under certain experimental conditions activity in arcs of two neurons is a prominent feature of cord activity. The facilitation and inhibition of activity in these direct pathways have been examined.

METHODS

Cats, either decerebrated or under light Dial anesthesia (Ciba, 0.4–0.6 cc/kg.) were used. The spinal cord was often transected at the lowest thoracic or the highest lumbar level. One or both dorsal roots and the ventral root on one side of either the seventh lumbar or the first sacral segment were prepared. Pairs of stimulating electrodes were applied to the dorsal roots. The proximal electrode in each case was 12 to 15 mm. from the cord. A second method of stimulation was through bipolar needle electrodes inserted into the gray matter. The discharge in ventral roots was led from electrodes placed sufficiently far from the cord to prevent appreciable complication of the record by the "electrotonic" ventral root potentials of Barron and Matthews (1936, 1938). The potential changes de-

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† A preliminary report of these experiments was made at the meeting of the American Physiological Society, New Orleans, La., March 15, 1940.

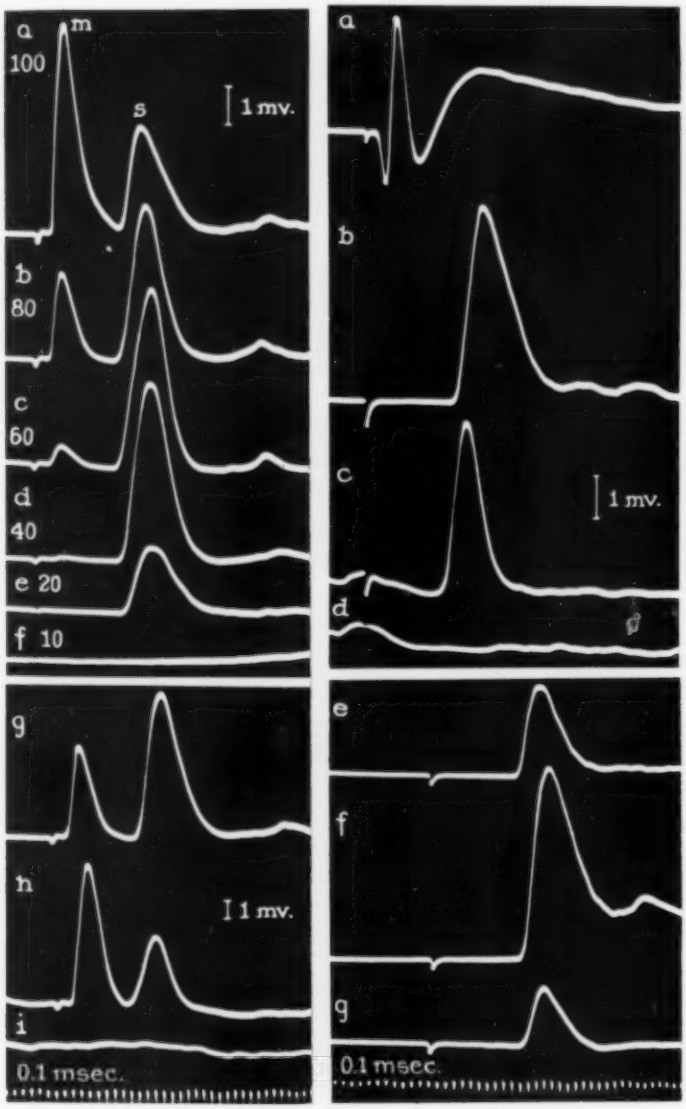

FIG. 1.(left). Ventral root discharge following stimulation by needle electrodes in the region of the intermediate gray matter. Decerebrated cat acutely spinal at the highest lumbar level. *a–f*, decreasing stimulus strengths, relative values indicated on the figure. *g–i*, the effect of conditioning the cord by a maximal dorsal root volley; *g*, needle stimulation; *h*, needle stimulation following a dorsal root volley by 3 msec.; *i*, end of response to dorsal root stimulation. Time, 0.1 msec.

FIG. 2 (right). *a*, cord potential, monopolar lead from the dorsum of the cord, stimulus a shock maximal for A fibers applied to the dorsal root. *b–g*, discharge in ventral root following stimulation of dorsal root. Same preparation as Fig. 1. *b*, discharge due to single maximal A volley. *c*, the same conditioned by a similar volley preceding by 3 msec. *d*, end of the response to the conditioning volley alone, showing baseline on which the response to the testing volley wrote. *e–f*, effect of DC polarization of the cord; current passed between the ventral root and muscles on the opposite side at the same level of the vertebral column. *e*, no current; *f*, 20 μA, root positive; *g*, 20 μA, root negative. Time, 0.1 msec.

veloped in the cord were recorded between an indifferently placed electrode and a small Ag-AgCl ball, 0.5 to 1.0 mm. in diameter, placed on the dorsum of the cord. For the determination of activity at points within the cord, the ball electrode was replaced by a micro-electrode which could be inserted into any desired position; use was made both of micropipettes and of fine steel needles insulated except near the tip. The customary stimulating apparatus and differential amplifier were used. The preparations were covered with paraffin oil to a depth of about one centimeter, in order to help maintain the cord and its roots at the proper temperature (*cf.* Table I) and otherwise in good condition for long periods of time.

Results

1. *Synaptic delay at motoneurons.* The synaptic delay at the motoneurons in the cord has been determined by a method originally used for another system by Lorente de Nó (1935d, 1939). Small bipolar needle electrodes were inserted into the cord, in order both to stimulate some motoneurons directly and to activate fibers and collaterals making synaptic connections with additional motor cells. The discharge in an adjacent, homolateral ventral root following such stimulation produces the two prominent waves that have been labelled *m* and *s* in Fig. 1 and 3. The threshold of stimulation for the *m* wave is lower than that for the *s* wave when the stimulating electrodes are in ventral positions within the cord—at or below the ventral horn. It is lower for the *s* wave when the electrodes are located more dorsally. The *m* wave represents a practically synchronous volley of impulses in fibers of the ventral root, and its latency is approximately accounted for by conduction from the cord to the recording electrodes. It therefore arises from direct electrical stimulation of the motoneurons.

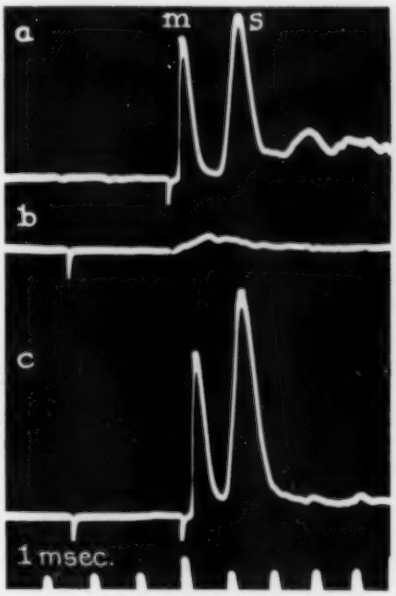

Fig. 3. Ventral root discharge following stimulation of the cord through needles in the central gray matter. Decerebrated cat, acutely spinal at the highest lumbar level. *a*, response to needle stimulation; *b*, to submaximal stimulation of the homolateral dorsal root; *c*, needle and root stimulation in combination. Time, 1 msec.

The *m* wave may be conditioned by the delivery of a previous shock to the dorsal root (Fig. 1*g–i*, 3). Since in the experiment from which the records of Fig. 1*g–i* are taken some motoneurons had responded to the conditioning shock, it might perhaps be thought that the increase in the *m* wave in record *h* is attributable to direct stimulation by the testing shock of additional motor fibers which were in a supernormal condition. This is scarcely possible, because the first motoneurons responded to the conditioning volley only 2.2 msec. (shock interval, 3.0 msec.) before the application of the test stimulus causing the *m* wave; and according to Gasser and Grundfest (1936) and Graham and

Lorente de Nó (1938) refractoriness gives way to supernormality in blood-perfused nerves only after 2 to 5 msec. Moreover, in the experiment of Fig. 3 facilitation of the *m* wave was observed without previous reflex discharge. Therefore, the facilitation of the *m* wave must be interpreted as due to a summation of the induction shock with subliminal synaptic stimuli (Lorente de Nó, 1935d; Lorente de Nó and Graham, 1938).

The *s* wave, which represents a somewhat asynchronous volley of impulses, follows the *m* at an interval of about 0.7 to 0.8 msec. As the stimulus is increased in strength from low values, both waves increase in size together until at high values the *s* wave decreases as the *m* wave continues to grow (Fig. 1*f–a*), obviously because motoneurons responding in the *s* group have

Table 1. Central reflex times and synaptic delays at motoneurous, determined together in several preparations

Experiment	Preparation	Rectal temperature	Cord temperature (Thermocouple)	Synaptic delay at motoneurons (msec.)		Central reflex time (msec.)	
				Unconditioned	Conditioned	Unconditioned	Conditioned
5/23/39	Decerebrated	38.0–38.4		0.7+	0.6	0.8–0.85	0.6–0.7
6/17/39	Decerebrated	36.8–37.8		0.9	0.65	0.9	0.7
6/27/39	Decerebrated	40.2–40.5	39.7 ± 0.2	0.8–	0.6–	0.65	0.5+
8/ 7/39	Decerebrated	40.0		0.9	0.7	0.85	0.7
10/10/39	Spinal	38.5		0.75	0.7	0.65	0.5

shifted to the *m* and become refractory. It is to be emphasized that the reduction of latency when motoneurons responding in *s* pass into *m* is not gradual but discontinuous. The interval between the two waves remains nearly constant over a considerable range of stimulus strengths and cannot be decreased by more than 0.1 to 0.3 msec., even when the cord has been conditioned by a maximal volley in the dorsal root (Fig. 1*g–i*). As a rule, the intervals between the feet of the *m* and *s* waves have ranged from 0.6 to about 1.0 msec. Since the conduction time for impulses exciting the motoneurons responding in the *s* wave must be small and since no procedures that have been tested reduce this interval significantly, it has been interpreted as representing the duration of one synaptic delay, *i.e.*, that at the motoneurons. The values obtained in several experiments are presented in Table 1.

2. *Central reflex time for homolateral reflex.* A close parallel exists between the results reported in the preceding section and observations made on central reflex times (see Table 1). The discharge in a ventral root, due to a volley maximal for most of the A fibers other than the delta group in the cor-

responding homolateral dorsal root, is usually characterized by an early wave (Eccles and Pritchard, 1937), with an unreduced latency of 1.0 to 1.4 msec. (Fig. 2 and 4). The well-known discharges which last 8 to 10 msec. or more often follow. The first wave may be small compared with the later phases, but usually it is the conspicuous deflection of the reflex oscillogram. The size of the intramedullary spike of the cord potential may be used as a rough measure of the number of A fibers stimulated. Judging on this basis, the appearance of the early wave generally requires the stimulation of $\frac{1}{4}$ to $\frac{1}{2}$ of the A fibers of the dorsal root. With weaker stimuli, responses of longer latency appear, and by varying the strengths of the testing and conditioning shocks applied to the dorsal roots, a continuous series of reflex latencies, ranging upward from the minimum, may be obtained.

The central reflex time is the observed reflex latency, minus conduction time in the afferent and efferent nerves. Conduction time in the dorsal roots has been measured as the interval between the stimulus escape and, as a good approximation to the time of arrival of impulses at the cord, the time corresponding to half the descent into the first positive trough of the primary spike of the cord potential (Fig. 2*a*). The latency of the *m* wave in such records as *a*–*c* of Fig. 1 has been taken as the conduction time in the ventral root. Since this correction is small and little altered by a considerable increase in the strength of the stimulus (Fig. 1*c*–*a*), the use of the shock-response interval for the determination of conduction time is justified. Except for about 3 mm. of the relatively stout "collatérales réflexo-motrices" (Cajal, 1909),

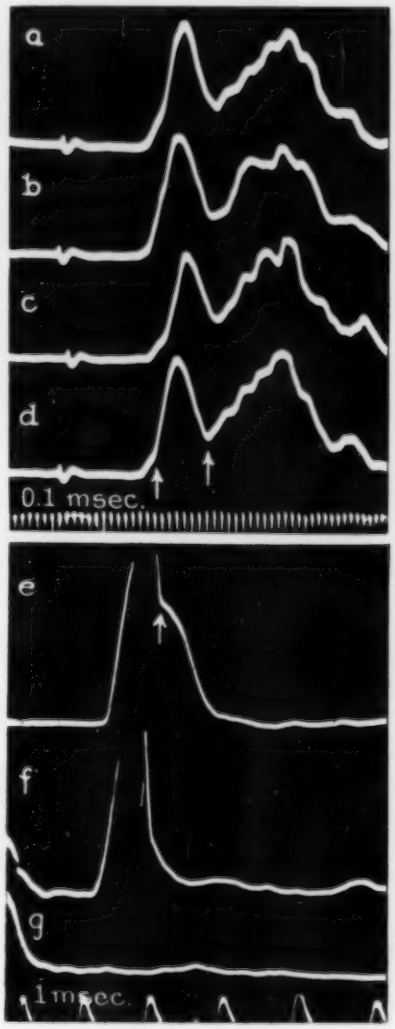

FIG. 4. Reflex discharges in ventral roots showing discontinuities in the populations of responding motoneurons. Discharges in ventral roots following the delivery of a single shock, maximal for A fibers, to the corresponding homolateral dorsal roots, *a*–*d*, decerebrated cat, acutely spinal at highest lumbar level. The corrections for conduction in the roots amounted to 0.4 msec. Discontinuities in the discharge occur at central reflex times of about 1.0 and 1.7 msec. Time, 0.1 msec. *e*–*g*, decerebrated cat. The corrections for conduction time in the roots amounted to 0.4+ msec. *e*, single testing volley; *f*, the same preceded by a similar volley; *g*, end of the response to the conditioning volley alone. Note the discontinuity in *e* at a central reflex time of about 1.7 msec. and its absence in *f*. Time, 1 msec.

which extend from the dorsum of the cord to the anterior horn, these corrections completely account for conduction time in the fast fibers of the direct reflex pathways.

In the experiment from which the records of Fig. 1 and 2 have been taken the corrections for root conduction are each about 0.2 msec. (Fig. 2*a*; 1*a–c*). The uncorrected latency of the first portion of the early wave of the discharge from the unconditioned cord is 1.05 msec. (Fig. 2*b*), giving a

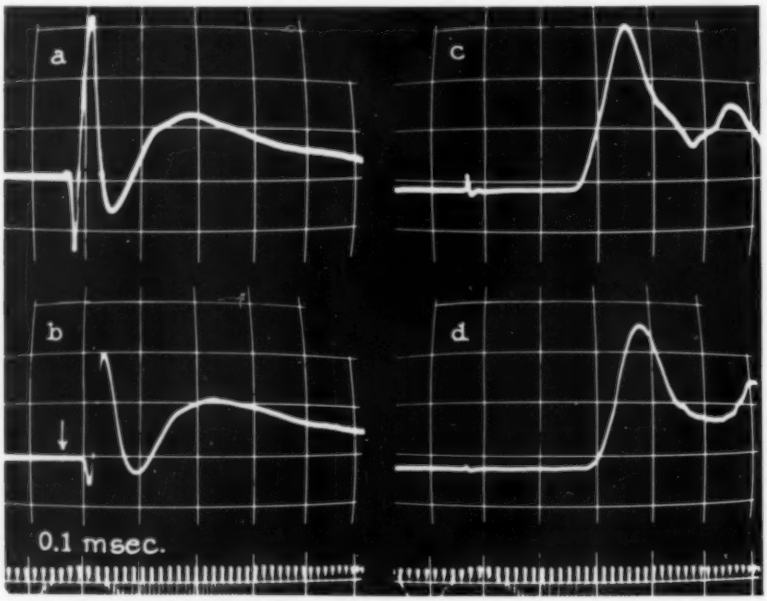

FIG. 5. *a*, *b*, cord potentials recorded from the dorsum of the cord; *c*, *d*, the corresponding reflex discharges in the ventral root. *a* and *c*, are responses to shocks applied to the dorsal root a few mm. from the cord; *b* and *d* are responses to stimuli applied 17 mm. more distally. All the shocks were 5 times the threshold for the intramedullary spike and the negative cord potential. Time, 0.1 msec.

central reflex time of 0.65 msec. As shown in Fig. 2*c*, this was reduced to about 0.5 msec. by a maximal conditioning volley preceding the testing in the same dorsal root by 3.8 msec. The data of several experiments are presented in Table 1.

The corrections for conduction time in the dorsal roots were based upon activity of the fastest fibers. The dorsal roots contain A fibers of a wide range of conduction velocities (Gasser and Grundfest, 1939), and the central reflex times as determined would be in error if activity in fibers conducting at significantly less than the maximum velocity were important for the reflex discharges. This possibility was tested in the following way (Fig. 5). Two pairs of stimulating electrodes were placed on a dorsal root, one pair near the cord and the other more distally. The distance between cathodes was 17

mm. The reflex discharges in the corresponding ventral root, and the potential changes at the dorsum of the cord, were recorded for graded series of stimuli applied through each pair of electrodes.

The shock-response intervals for various points on the first portion of the intramedullary spike which followed distal stimulation were greater than the corresponding intervals for proximal stimulation (Fig. 5*a*, *b*). The difference indicated a maximal conduction velocity in the dorsal root of about 80 m. per sec., which approximates the known value for the fastest sensory fibers. The latency of each point of the early part of the reflex discharge to stimulation via the distal electrodes was also greater than that to stimulation through the proximal electrodes (Fig. 5*c*, *d*), and by an interval equal to or only slightly longer than the conduction time between the cathodes for the fastest afferent fibers. If activity in fibers of significantly submaximal velocity were important for the earliest discharges, then parts or all of the first wave of the reflex to distal stimulation would have appeared only after a greater delay.

In view of these data it is conservative to state that the first portions of the reflex discharge are due to activity in A fibers conducting at velocities ranging between maximal and no less than two-thirds maximal. The corrections for conduction time in the dorsal roots, based upon activity in the fastest fibers, amounted to about 0.2 msec. For fibers conducting at two-thirds the maximal velocities the corrections are increased by only 0.1 msec. Accordingly, the corrections as used cannot be in serious error.

These observations incidentally provide conclusive evidence that the stimuli applied to the dorsal roots did not spread to cause direct excitation of central structures.

An attempt further to shorten the central reflex time by polarization of the cord with constant currents, has failed. Barron and Matthews (1936, 1938) and Matthews (1937) have shown that the passage of small currents from a motor root to an adjacent point on the spinal cord causes a rhythmic discharge in fibers of the ventral root at frequencies up to 70 per sec., depending upon the strength of the current. No discharge occurs when the current is passed in the opposite direction, *i.e.*, cathode on root. Figure 2*e–g* demonstrates that in fact very small direct currents, too weak to cause appreciable rhythmic discharge, nevertheless condition the cord. Figure 2*e* shows a central reflex discharge recorded with no current flowing, 2*f* the augmented response obtained when a current of 20 microamperes was passing from a point on the ventral root to an electrode placed on muscles of the contralateral side at the same level of the vertebral column, and 2*g* the reduced response seen during the passage of 20μA in the opposite direction. A current of 10μA was sufficient to produce smaller but definite effects of the same nature. Although in Fig. 2*f* the augmentation of the response is considerable, no appreciable decrease in latency occurred.

3. *Conditioning of first wave of homolateral reflex by single contralateral volley.* The data of the previous sections have been interpreted as demon-

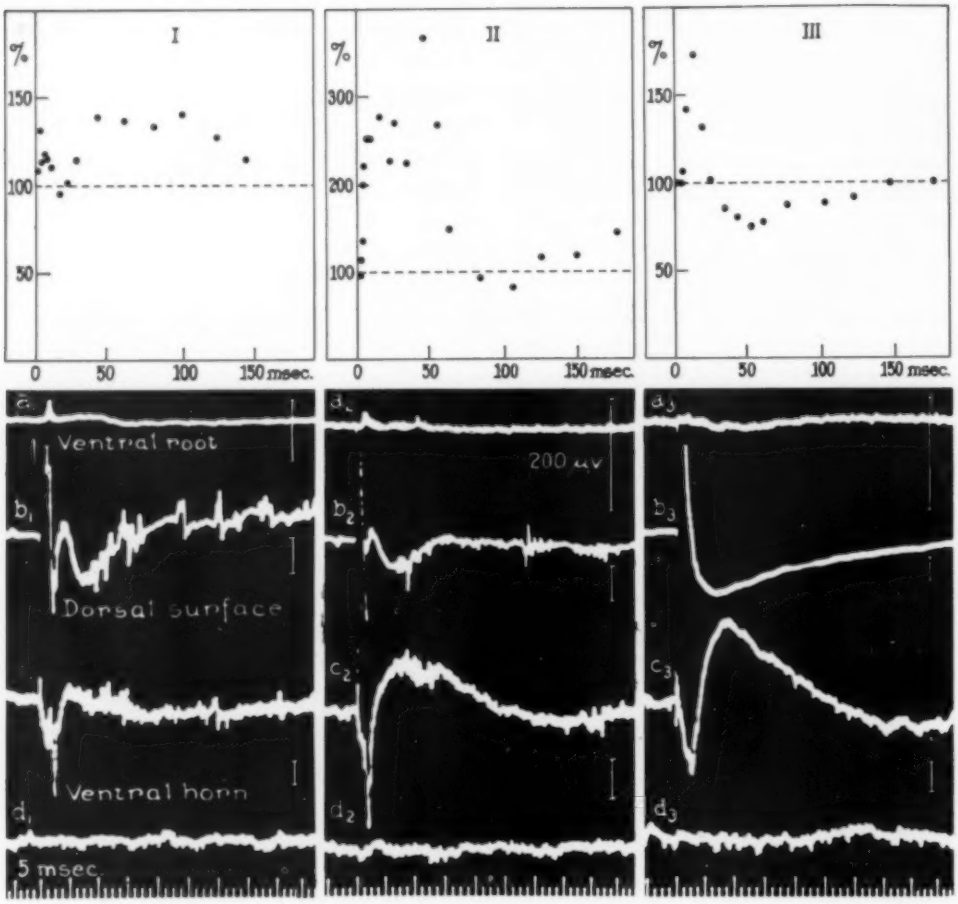

FIG. 6. Conditioning of the first wave of the dorsal-to-ventral root reflex by a single crossed volley. Data from three spinal cats, I and II decerebrated, III under light Dial narcosis. Abscissae of the graphs: intervals at which the homolateral stimulus followed the contralateral. Ordinates $\frac{\text{height of conditioned first wave}}{\text{height of unconditioned first wave}} \times 100$. The oscillograms show the responses to the crossed volley alone: *a*, reflex discharge in ventral root; *b*, potential changes recorded from the mid-dorsum of the cord; *c*, potential changes recorded by a micro-electrode in the ventral horn; *d*, as *c* but without the stimulus, to show the background of spontaneous activity. Voltage calibrations, 200 μV. Time, 5 and 20 msec.

strating that the early wave of the reflex discharge is a measure of activity in arcs of two neurons (see Discussion). Consequently there becomes available a convenient method for testing the average synaptic excitability of the motoneurons in the pool supplied by the stimulated dorsal root fibers; for these motoneurons may be directly stimulated at any chosen moment by a controlled afferent volley which produces a measurable submaximal discharge.

The conditioning of the first wave of the homolaterally evoked reflex by a single contralateral volley has been examined in a series of 23 spinal cats. Figure 6 presents data obtained from three of these. In addition to the conditioning curves, the figure includes oscillograms to show that a small reflex discharge is evoked by the contralateral volley. Also included, as indices of the internuncial activity induced by the contralateral volley, are records of the cord potentials produced by it on the mid-dorsum of the cord and in the ventral horn.

The conspicuous effect of a single crossed volley on the reflex activity of a flexor muscle is typically inhibition (Samojloff and Kisseleff, 1927; Eccles and Sherrington, 1931b; Hughes, McCouch and Stewart, 1937). Under the conditions of the present experiments, however, the early reflex discharges in the ventral roots of the majority of active, decerebrated preparations are facilitated by the contralateral volley. The facilitation may amount to several hundred per cent and last for 150–200 msec., as in curves I and II of Fig. 6. Other preparations, including nearly all animals under light Dial narcosis, yield conditioning curves in which facilitation gives way after 10–25 msec. to a more prolonged period of inhibition (curve III). The maximal inhibition occurs 30–50 msec. after the contralateral stimulus; at this time the height of the first wave of the conditioned testing volley is reduced to 50–80 per cent of its unconditioned size.

Discussion

The similarity of the values for the shortest central reflex time and the interval between the *m* and *s* waves (Table 1) demonstrates that the earliest reflex discharges represent activity in the direct pathways which have only a single synaptic relay; and the fact that it has not been possible to reduce either the central reflex time or the *m–s* interval below about 0.5 msec., suggests that this is a minimal value for the synaptic delay at the motoneurons.

The question that next arises, is, how *long* may be the synaptic delay? The central reflex times obtained for conditioned and unconditioned reflex responses to dorsal root volleys of varying size represent a series, continuous to the precision of the measurements, extending from 0.5 msec. to 2 msec. or more; and in many experiments in which the first motoneurons respond at the shortest central reflex times there is clear evidence that others become active at progressively longer intervals. The long latencies do not necessarily signify prolonged synaptic delays, however, and considerable evidence favors the alternative view that they represent activity in arcs containing interneurons (Lorente de Nó, 1938b). It is known that interneurons are present. They may be interpolated between the dorsal root fibers and the motoneurons to form reflex arcs of two, three and more synaptic relays; and they are activated by afferent impulses (Gasser and Graham, 1933; Hughes and Gasser, 1934a). A synaptic delay is properly measured from the time of arrival of the latest impulse which is effective in firing the post-synaptic

neuron. Hence, because of the probability that motoneurons are effectively stimulated by the delayed internuncial impulses, it is difficult to determine the maximal central reflex times associated with activity in the direct pathways. It may only be stated that the range of latencies must extend from 0.5 msec. upward to at least the minimal central reflex time for activity in three-neuron arcs. This shortest central reflex time for pathways of three neurons can be no less than the sum of the minimal delay at a motoneuron and the minimal delay at an interneuron. The duration of the delay at interneurons thus becomes a matter of interest.

The available evidence suggests that 0.5 msec. is an approximate minimal value for the delay at interneurons, as well as at motoneurons. Inspection of Fig. 2*a*, which represents the potential changes produced at the dorsum of the cord by an afferent volley, shows that the curve crosses the baseline to rise into the negative cord potential (Gasser and Graham, 1933) only 0.6 msec. after the impulses in the dorsal root fibers have reached the cord. This suggests that 0.6 msec. is an upper limit for the synaptic delay at the earliest responding interneurons. Stewart, Hughes and McCouch (1940) report slightly longer latencies in the monkey. Similar short delays have been found in other parts of the nervous system. Lorente de Nó (1939) reports that in the internuncial nuclei associated with the oculomotor nucleus the synaptic delays correspond to those at the motoneurons; that is, they may be as short as 0.5 to 0.6 msec. The results of Bishop and O'Leary (1938) indicate a delay of 0.5 msec. for visual impulses relayed at the lateral geniculate body; and Kemp, Coppée and Robinson (1937) have calculated the slightly longer minimal value of 0.8 msec. for impulses relayed in the auditory pathways at the cochlear nucleus and the olivary complex.

The sum of the shortest synaptic delays that have been determined for interneurons and motoneurons, each 0.5 msec., is 1.0 msec. Accordingly, unless internuncial delays of unsuspected brevity occur in the cord, 1.0 msec. must be the minimal central reflex time for activity in three-neuron arcs. Therefore, all central reflex times of from 0.5 msec. to 1.0 msec. must pertain to arcs of two neurons. With one reservation, the synaptic delays at the motoneurons must extend over this range of values. The reservation arises from the fact that the time for conduction in the 2–3 mm. of collateral within the cord was not considered; and, of course, the corrections for conduction time in the dorsal roots were based upon activity in fibers conducting at maximal velocities. The early part of the reflex is mediated only by fibers conducting at velocities near the maximal; the stoutness of the collaterals of these large sensory fibers (*cf.* Cajal, 1909) justifies the assumption that they do not conduct at low velocities. Consequently these factors can contribute at most an additional 0.1 msec. to conduction time, and 0.9 msec. becomes a conservative *minimal* value for the longest synaptic delay at motoneurons of the cord. At present it is not possible to state whether still longer delays occur.

Little is known of the range of variation of the delays at interneurons,

but if it be assumed that the interpolation of an interneuron into a reflex arc increases the central reflex time by an amount likewise varying between 0.5 and about 1.0 msec., then the central reflex times for three-neuron pathways can vary between 1.0 and 2.0 msec., for four-neuron pathways between 1.5 and 3.0 msec., and so forth. Motoneuron discharges, such as may be observed at all reflex times longer than the minimum, can therefore be accounted for. At the same time it becomes apparent that, except for the earliest discharges, the number of synaptic relays involved in the production of any reflex activity cannot be strictly calculated from the central delay. It is impossible, for example, to state whether motoneurons firing after a central time of 2.4 msec. represent activity in pathways of three synaptic relays with an average delay of 0.8 msec., or in arcs of an additional relay where the average delay amounts to only 0.6 msec., or in both.

Although some motoneurons may be fired at each moment during the period of reflex activity, the discharges do not give smooth curves. As reference to any actual record brings out, the synaptic delays gather about modes, and the motoneurons, especially in the early part of a discharge, tend to be fired in groups. Hence for the first portions of a discharge it is possible to make a fairly exact estimate of the number of synaptic relays involved.

The reflex discharges in the records of Fig. 4 exhibit typical grouping of the responding motoneurons and show the discontinuities which consequently appear at characteristic central reflex times. The discharges following four identical afferent volleys in a single experiment are shown in Fig. 4*a–d*. It is obvious that the grouping of responding units is relatively constant. At a central reflex time of 1.0 msec., as marked by the first arrow, the number of active units increases. Again at 1.7 msec., as indicated by the second arrow, the discharge is suddenly augmented. The second wave follows the first at an interval of 0.7–0.9 msec., the duration of an average synaptic delay. Figure 4*e* depicts the reflex discharge from another experiment. Activity begins after a central reflex time of 0.9 msec. and, as marked by the arrow, is also characterized by a discontinuity at about 1.7 msec. The activity following the discontinuity is largely abolished in the conditioned response shown in Fig. 4*f*, whereas the discharges at shorter reflex times behave as a homogeneous group and are somewhat increased.

In some experiments (Fig. 2*b*) the first wave of the reflex discharge is due almost entirely to activity of motoneurons which respond at central reflex times of 1.0 msec. and less. In the experiments of Fig. 4, however, the first wave represents the activity of motoneurons which fire at intervals ranging from 0.8 and 0.9 msec. to more than 1.0 msec., in fact to about 1.2 msec. The portion of the first wave which corresponds to central reflex times of 1.0 msec. and less must of course represent activity in arcs of two neurons. It cannot at present be stated with finality that the motoneurons which discharge in the later portion of the first wave have not been activated via an interpolated interneuron, rather than directly by the primary afferent fibers. At any rate, on conditioning the first wave behaves more or less as a

unit in facilitation and inhibition. Hence, if an interneuron is interposed, it must be one which follows the activity in the afferent fibers very nearly in a 1:1 ratio under various conditions. This hypothetical behavior is in contrast with that of the spinal interneurons which have been studied, for it is well known that these respond subnormally after a conditioning volley (Hughes and Gasser, 1934b).

The possibility of exciting motoneurons directly by a controlled afferent volley, the size of which does not vary with the level of excitation in labile internuncial systems, provides an excellent method for testing the average synaptic excitability of the motoneurons in the pool supplied by the stimulated dorsal root fibers. Illustrative experiments, in which the synaptic excitability of the motoneurons was tested at various intervals after the delivery of a contralateral volley to the cord, reveal the action of mechanisms for facilitation and inhibition which have been described by Gasser (1937a, b), Hughes and Gasser (1934b), and by Lorente de Nó (1935c, 1936, 1938b, 1939).

Although the contralateral volley fires few motoneurons, it facilitates others, and the direct response to a homolateral volley is increased for a period of time, as in all three curves of Fig. 6. In most decerebrated preparations the facilitation is long continued, as in curves I and II, with at most only transitory intervention of slight inhibition. In other experiments, particularly when a light dose of Dial is given, the facilitation passes over into inhibition after 10–25 msec., as in curve III.

The potential changes produced in the ventral horn by the crossed volley reveal a mechanism for the facilitation. Although the significance of the envelope to the sequence of potential changes is not yet clear, the width and roughness of the baseline may be used as indices of the level of background activity. Comparison of records *a* with *c* and *d* (Fig. 6) reveals that even in the ventral root lead, where recording is more favorable than in the volume of the cord, the active motoneurons produce relatively small deflections compared to the changes observed in the ventral horn. Consequently most of the background activity of the ventral horn must be interneuronal. At least some of the internuncial impulses must ordinarily impinge upon the motoneurons. The periods during which the testing two-neuron discharge is facilitated are characterized by an increase of the background of internuncial activity above its resting level (records *c*, also *b*). Facilitation, therefore, is accomplished by convergence of internuncial impulses with the primary testing impulses.

During inhibition (curve III) the deficit in the response of the two-neuron arcs must be due, at least in part, to subnormality in the few motoneurons which were fired by the contralateral volley. Antidromic stimulation has revealed that, following activity, motoneurons exhibit a prolonged period of lowered synaptic excitability (Eccles, 1931; Lorente de Nó, 1935b, 1939; Gasser, 1939).

Subsequent experiments have shown that, although in spinal animals most of the

unconditioned discharge of short central latency goes to flexor muscles, some impulses are in fibers to extensors. Also, in acutely spinal animals the contralaterally evoked impulses do not necessarily represent a discharge only of motoneurons associated with extensor muscles (McCouch, Snape and Stewart, 1935, McCouch, 1936).

For the sake of completeness it may be mentioned that the conditioning volleys must have evoked crossed dorsal root reflexes. The centrifugal impulses of these discharges may have interfered with and blocked centripetal impulses of the testing volleys. Any such modification of large testing volleys must be slight, for crossed dorsal root reflexes are small and dispersed discharges (Toennies, 1938).

The cord potentials produced by the contralateral volley in the ventral horn point to the existence of a second factor for inhibition. Subnormality in interneurons may be expected to follow the increased activity which characterizes the antecedent period of facilitation; and, in fact, during the period in which the testing two-neuron discharge shows a pronounced deficit (curve III), the background of internuncial activity is decreased below the resting level (record c_3). Withdrawal of the facilitating effect of these impulses may raise the threshold of the motoneurons and aid in the production of the observed deficit.

Summary

A shock which excites ¼ to ½ of the fibers of maximal and nearly maximal conduction velocity in the seventh lumbar or the first sacral dorsal root of the decerebrated cat typically produces in the corresponding homolateral ventral root a reflex discharge with a central delay varying between 0.65 and about 1.0 msec. Conditioning the cord by means of a previous dorsal root volley may decrease the central reflex time slightly, but no procedures have reduced it below about 0.5 msec. Ventral root discharges resulting from direct electrical stimulation of the central gray matter demonstrate that the synaptic delays at the motoneurons vary over a similar range of values. Consequently central reflex times of 0.5 to about 1.0 msec. represent activity in reflex arcs of two neurons (one synaptic relay). It is not possible to state whether or not longer synaptic delays sometimes occur, for central reflex times as short as about 1.0 msec. may conceivably pertain to activity in arcs of three neurons.

Motoneurons may respond at any or all central reflex times for several milliseconds after the first discharge to a dorsal root volley—a result to be expected even if the synaptic delays at interneurons as well as at motoneurons range between limits no wider than 0.5 to 1.0 msec. Nevertheless, the synapse times show modes, and large groups of motoneurons are typically discharged at particular central reflex times.

Direct excitation of motoneurons by the primary sensory fibers offers a method of testing the synaptic excitability of the motoneurons. The motoneurons are facilitated for some time after the arrival at the cord of a volley over a contralateral dorsal root. During the period of facilitation, as can be determined from cord leads, the motoneurons are receiving a barrage of impulses from interneurons. Facilitation, therefore, is accomplished by convergence of internuncial impulses with the impulses of the testing volley. A

period of inhibition sometimes follows the facilitation. The inhibition must be attributable, at least in part, to subnormality in the few motoneurons which were fired by the crossed volley. An additional factor for inhibition may be subnormality in the neurons of internuncial systems which tonically barrage the motoneurons; for following the increased activity of the period of facilitation, the number of internuncial impulses impinging upon the motoneurons is reduced below the resting level.

It is a pleasure to express my appreciation to Dr. Herbert S. Gasser and to Dr. Rafael Lorente de Nó for their advice and helpful criticism during the course of this work.

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INFLUENCE OF SENSORY SYSTEMS ON SPONTANEOUS ACTIVITY OF CEREBRAL CORTEX[1]

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THE INFLUENCE of the sensory systems of the body upon the electrical activity of cortical brain cells is manifest in a number of different ways. The simplest case is the discrete response which stimulation of a sensory nerve evokes in the cortical cells upon which the sensory tracts directly project. By utilizing such responses the areas of the cortex concerned in specific modalities of sensation have been mapped for visual and auditory, as well as for somatic sensation from the various regions of the body (3, 6).

Afferent stimulation also affects the grouping of the *spontaneous* activity of the cortical cells, as seen in the temporary interruption of the rhythmical discharges on illumination of the eyes. But even more important influences upon the spontaneous activity have been demonstrated by deafferentation of the cortex. Bishop (4) showed that in the rabbit under Dial narcosis, separation of the cortex from the thalamus abolished the 5 per sec. rhythm of the cortical cells, leaving a more rapid rhythm intact. Because of this and other similar evidence Bishop attributed the characteristic rhythmicity of the spontaneous cortical discharges to a synchronization by impulses traversing cortico-thalamo-cortical circuits. Bremer (5), found that section of the afferent pathways *below* the level of the thalamus also modified the cortical discharges. "Isolation" of the brain of the cat under ether, by transection of the brain stem, changed the fast, regular discharges characteristic of ether anesthesia to grouped periodic bursts of activity.

Under certain conditions of deep anesthesia the influence of the afferent mechanisms is also clearly evident. Adrian (1) found that stimulation of sensory nerves in the rabbit under Dial increased the frequency of spontaneous cortical discharge. We observed a similar effect in the cat under nembutal (10); and in addition, the increased activity occurred throughout the greater part of the cortex. We found also under nembutal anesthesia that separation of the cortex from the afferent pathways at levels above or below the thalamus (or destruction of the thalamus itself), completely abolished cortical activity. These experiments showed definitely that the spontaneous activity of the cortical cells depended in the circumstances on integrity of sensory pathways.

Forbes and Morison (8), recently reported experiments on the cat which led them to essentially similar conclusions. They advanced evidence that the spontaneous activity of the cortex under nembutal anesthesia had its

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origin in subcortical, possibly thalamic centers. On stimulating sensory nerves they observed a simple "primary" response in the true sensory areas, and a "secondary" response wide-spread over the cortex. Since the "secondary response" appeared identical with the spontaneous activity, both in character and in distribution over the cortex, they felt that both had a common origin in subcortical centers.

From the studies of these various investigators it seems clear that the afferent fibers to the cortex can not only initiate discrete cortical responses, but can modify and perhaps determine the pattern of grouping of the rhythmical activity which is so characteristic of cortical cells. In the experiments herein reported we have attempted to analyze the influence of the afferent systems on the spontaneous cortical activity. These studies are an extension of work reported earlier (10).

METHODS

Nembutal (sodium pentobarbital), 40–50 mgm. per kg. was administered subcutaneously to cats and the brain exposed widely. Leads were taken from various parts of the cortex, but oftenest well back on the posterior ectosylvian gyrus. Silver-silver chloride electrodes were connected to a suitable amplifier and the potentials recorded photographically in the usual manner by means of a Matthews oscillograph.

In some experiments ether or chloralose anesthesia was used. However, unless other anesthesias are specifically mentioned, the results described below apply to the cortex under nembutal. Sensory nerves and sensory pathways were stimulated by a device by which condenser discharges could be applied at varying strength and frequency. Special care was taken to preserve the circulation of the cortex during the various operations. This is particularly important in decerebration; a lateral approach to the brain-stem proved the best way to avoid injury of the larger blood vessels of the stem. To stimulate the thalamus, either one cerebral hemisphere was removed, or the corpus callosum was divided and electrodes put down on the surface of, or into the thalamus. The thalamic radiations were reached by the same approach.

RESULTS

When the cortex is inactive in the sense of showing little electrical activity (as it is under *deep* nembutal anesthesia), cellular discharges can be initiated by rhythmical, slow, single-shock stimulation of sensory nerves. If the sciatic nerve is stimulated at rates between 6 and 20 per min., a cortical response resembling the grouped discharges of spontaneous bursts eventually occurs after each stimulus. Once initiated, these trains of activity may continue at the frequency of the previous stimuli for several minutes after the end of stimulation. They only gradually subside and finally disappear. It is clear that under these circumstances stimulation of sensory nerves initiates the cortical activity, and is necessary moreover, to maintain continual activity.

If the cortex fires spontaneously, as occurs under lighter anesthesia, the grouped trains or bursts of activity which are characteristic of nembutal anesthesia, appear more frequently during stimulation of a sensory nerve. Stimulation of the sciatic nerve at rates between 6 and 20 per min. results in a burst usually after each stimulus (Fig. 1). With higher frequencies the bursts appear either after alternate stimuli or at shorter intervals than be-

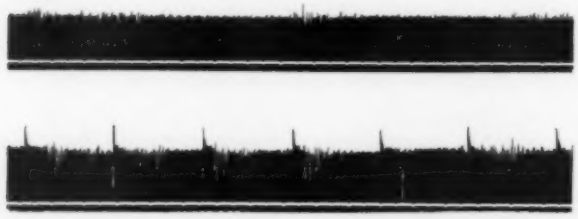

FIG. 1. Cortical response to stimulation of left sciatic nerve. Leads from right ectosylvian gyrus. Upper record control showing spontaneous activity. Lower record, stimulation at 11 per min., stimulus artefact followed by burst of activity resembling the spontaneous discharges. Cat under nembutal. Time, 1 sec.

fore, but with no definite relation to the individual stimuli (Fig. 2). In either case afferent stimulation increases the number of bursts per second and thereby the total activity of the cortex.

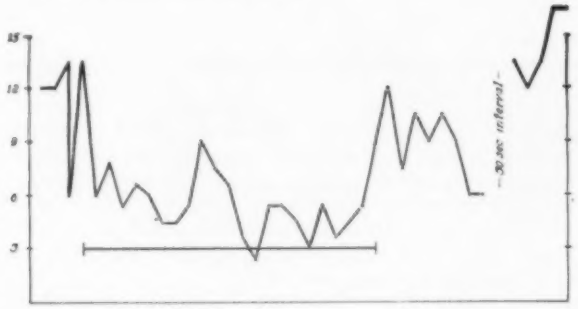

FIG. 2. Graph showing effect of stimulation of optic thalamus on cortical activity. Ordinate indicates time in seconds from onset of one grouped burst of activity (as shown in Fig. 1) to beginning of next. Each dot represents a grouped discharge. Horizontal bar marks period of stimulation of right optic thalamus at frequency of 20 per min. (once in 3 sec.). The frequency of the bursts is increased but there is not a response to each stimulus. Leads from right sigmoid gyrus. Cat; nembutal anesthesia.

After several minutes of increased activity from stimulation the cortical bursts characteristically fall back to their previous frequency, even though stimulation be continued. After the end of stimulation a long period of inactivity usually follows. These results from stimulation of a peripheral

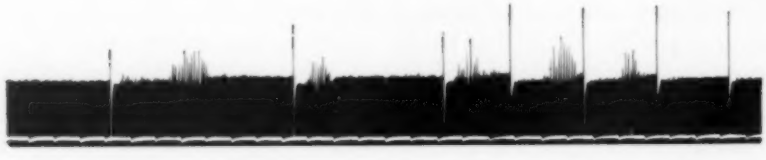

FIG. 3. Cortical response to stimulation of the ipsilateral optic thalamus. Leads from sigmoid gyrus. Opposite hemisphere removed. Stimuli at varying frequencies; failure after 5th response. Time, 1 sec. Cat under nembutal.

nerve can be duplicated by stimulating the trigeminal nerve. Furthermore, stimulation of the central afferent systems, *e.g.*, the optic thalamus (Fig. 2 and 3) and the thalamo-cortical pathways also induces responses which have the same characteristics.

The cortical response to slow sensory stimuli is always, under the conditions of our experiments, a burst of activity. The effect appears quite generally over the whole cortex. Furthermore, records from the two hemispheres appear similar even if the sciatic nerve is stimulated on one side only. The form of the burst is apparently quite similar in all parts of the cortex from the frontal poles back to the occipital poles and from the longitudinal fissure down to the temporal lobe.

These wide-spread discharges set up by this type of slow sensory stimulation have a pattern identical with that of the spontaneous bursts. It appeared to us that the stimulation increased the rate of the spontaneous activity, rather than set up a new or different kind of response. This inference

FIG. 4. Response of cortex to stimulation of optic thalamus at high frequency between arrows (30 per sec.) resembling the discharges in human cases of epilepsy. Gradual build up of "cusp and dart" pattern. Time, 1 sec. Cat decerebrated under ether by section of brain-stem at colliculi; one hemisphere removed. Leads from ectosylvian gyrus.

is strengthened by the fact that the spontaneous bursts appear likewise identical in all the various cortical areas examined, as Forbes and Morrison pointed out. Such similarity in form and distribution of the spontaneous and induced bursts naturally raises the question whether their similarity is caused by some common mechanism.

While the cortical response to single shocks applied to sensory pathways is a burst of activity similar to the spontaneous bursts; prolonged stimulation elicits a different type of discharge. When sensory nerves are stimulated at higher frequencies (40 to 60 per sec.) for 1–5 sec., a long after-discharge follows. The pattern resembles that following prolonged direct stimulation of the cortex itself as described by Adrian (2), Dusser de Barenne and McCulloch (7), and Larrabee and Hendrix (9). Though the form of this after-discharge is unlike that of the spontaneous burst, its distribution over the cortex is the same since it is wide-spread and similar in various areas. Hence, the pattern of afferent stimuli seems to determine the character of the response; but the greater part of the cortex responds, regardless of the type of stimulation.

Stimulation of the thalamus and the optic radiations at higher frequencies likewise produced similar results. There were certain exceptions: In a few animals which had been decerebrated under ether, but under conditions which we could not readily determine, a prolonged after-discharge of the kind seen in epileptic patients occurred from stimulating the optic thalamus

(Fig. 4). We include this observation because of the implication that such a discharge may be initiated from subcortical levels.

These experiments suggest that under nembutal anesthesia the cortical discharges, both spontaneous and induced, are motivated by the activity of

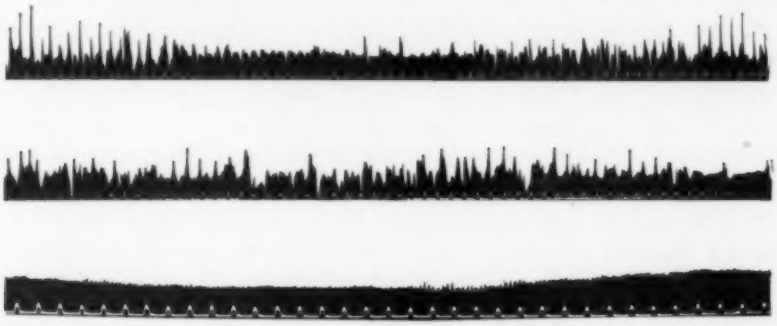

FIG. 5. Effect on spontaneous cortical activity of successive transections of upper cervical cord (middle record) and pons below 5th nerve (lower record) Upper, control. Decrease in size of spikes but preservation of grouped character. Nembutal anesthesia. Time, 0.2 sec.

sensory systems. We, therefore, studied next, the effects on the cortical activity of separating the afferent pathways at different levels of the tracts from the cortex.

Successive transections from below upward through the spinal cord, medulla and pons, causes a progressive diminution in size of the cortical discharges, but their grouped character remains unchanged (Fig. 5). On the other hand, transection of the brain-stem at the level of the colliculi, completely abolishes all cortical activity (Fig. 6). The same result follows de-

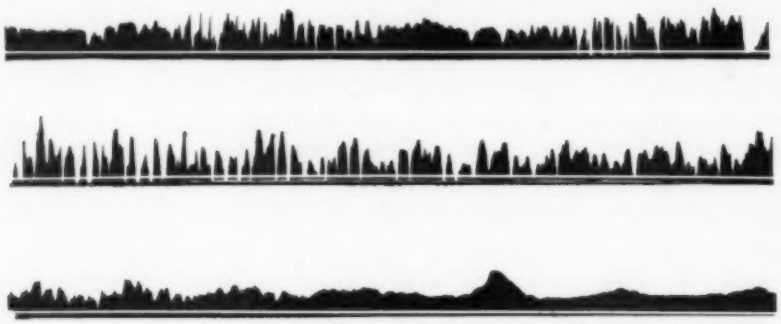

FIG. 6. Effect of transection of brain-stem between colliculi on spontaneous cortical activity of cat under nembutal. Upper record, control; middle, immediately after transection; lower, 26 sec. after section showing complete failure of cortical activity.

struction of the posterior part of the optic thalamus, or transection of the thalamo-cortical fibers in the internal capsule.

This abolition of cortical activity appears specifically due to destruction of the sensory pathways. Removal of the cerebellum, or of one cerebral

hemisphere and the frontal and occipital poles of the other, did not abolish the grouped discharge. Indeed, if all of the cortex was removed except a thin slice some 5 mm. wide, this remnant still showed typically-grouped discharges so long as it was connected to the thalamus. Furthermore, grouped discharges occurred in it on stimulation of a sensory nerve. Interruption of the thalamic connections, however, immediately stopped the discharge.

The abolition is apparently not caused by the shock of the operation of transecting sensory paths, for the more extensive operations described above have no such effect. Nor is it due to a fall in blood pressure, for the same pro-

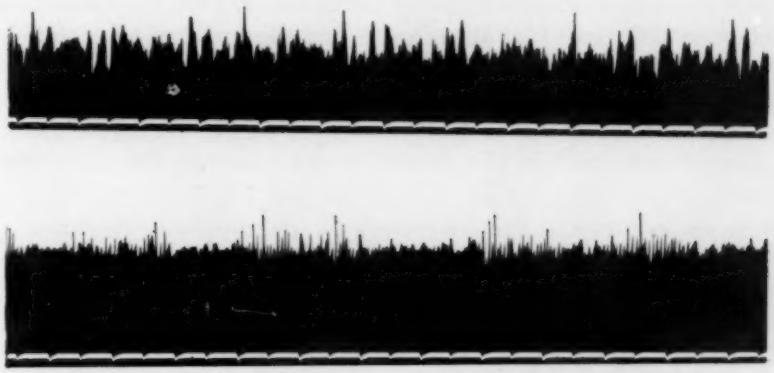

FIG. 7. The same procedure as in Fig. 6, but under ether anesthesia. Upper, control; lower, after section. The discharges become grouped but do not disappear. Time, 1 sec.

cedure under ether does not abolish the discharge. Furthermore, transection of the midbrain is not likely to cause further fall in blood pressure after the medulla has previously been cut across; yet the first mentioned procedure abolished the spontaneous discharge. Finally, the cortex was stimulated electrically, in some experiments, showing it was viable. It therefore appears to us that shock or failing circulation is not responsible for the failure of cortical discharges on transection of the afferent pathways.

The marked dependence of the activity of cortical cells on their afferent connections is due, in this case, to depression caused by the deep nembutal anesthesia. In a few experiments under lighter nembutal anesthesia the discharges reappeared after transecting the brain-stem, but they were always much reduced in size. Moreover, under other anesthetics, section of afferent pathways does not abolish the activity but only modifies it. We have confirmed Bremer's observation that under ether transection of the cat's brain-stem between the colliculi changes the fast regular rhythm to periodic grouped discharges (Fig. 7). We have found a similar modification following transection of the thalamo-cortical pathways under ether anesthesia.

DISCUSSION

These experiments show that the spontaneous activity of the cortex under deep nembutal anesthesia is dependent on the integrity of the af-

ferent systems. Destruction of the afferent pathways or of the thalamus abolishes the discharges all over the cortex. Slow stimulation of afferent pathways sets up bursts of activity which appear to us identical with the spontaneous activity both in form and in wide-spread distribution over the cortex. This marked dependence of cortical cells on afferent connections is obviously related to the special character of the anesthetic used. Under ether the cortex is considerably less dependent on the afferent fibers, for it continues to fire when these are severed. But the effect, even here, is seen in the altered character of the spontaneous activity. The refractory period of cortex and thalamus under ether and nembutal is further evidence of a differential action of these two anesthetics and may account for the character of our results. Marshall (11) found a much longer relative refractory period for nembutal than for ether.

The resemblance of the activity set up by afferent stimulation to the spontaneous bursts both in the general pattern and in the wide-spread distribution over the cortex led us to conclude that the result of afferent stimulation was an increase in the frequency of the spontaneous bursts. Forbes and Morison (8) describe these generalized bursts following sensory stimulation under nembutal anesthesia as "secondary responses," while we have considered them as increased spontaneous activity. Both we and they presume that these bursts are elicited from and shaped in the afferent systems. Forbes and Morison suggest that they originate in afferent centers, perhaps in the thalamus, rather than spreading from primary sensory cortex outward. In our experiments destruction of the thalamus stopped the cortical discharges; but obviously the thalamus cannot originate the discharges unless it receives afferent impulses from the brain-stem, for transection of the stem also abolishes the cortical discharge.

All the evidence of our own experiments and of the other workers quoted above points to the fact that the pattern of the rhythmical spontaneous cortical activity is shaped under the influence of afferent impulses to the brain. Our observations and those of Forbes and Morison emphasize the importance of this afferent control over the activity of the totality of the cortical cells. It cannot be doubted that other influences share in the synchronization of the cortical discharges; intercortical connections almost certainly play a part under normal circumstances (Adrian, 2).

Nembutal minimizes these other factors and by its specific action brings clearly to light the dominant influence of the sensory systems of the body on the generalized cortical activity.

Summary

The activity of cortical brain cells in cats under deep nembutal anesthesia disappears on transection of the brain-stem at the colliculi, on destruction of the optic thalamus, or on cutting the thalamocortical radiations. Removal of the cerebellum, the opposite hemisphere, the occipital and the frontal pole does not abolish the discharge in the remaining cortex. Separa-

tion of the cortical connections to the thalamus, however, promptly stops the activity. These observations show that under nembutal anesthesia the spontaneous activity of the cortex is dependent upon the integrity of the sensory pathways.

Stimulation of sensory nerves, of the thalamus, or of thalamocortical fibers at rates between 6 and 20 per min. evokes, under nembutal, discharges which appear like the spontaneous bursts of activity, both in pattern and in widespread distribution throughout the cortex. Stimulation at faster rates (16 to 20 per sec.) for 1 to 5 sec. sets up an after-discharge lasting several minutes. This also is wide-spread throughout the cortex.

These two lines of evidence show the importance of the sensory systems of the body in shaping the character of the continuous spontaneous activity of cortical brain cells.

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CHOLINE ESTERASE IN BRAIN AND SPINAL CORD OF SHEEP EMBRYOS

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INTRODUCTION

IT HAS BEEN shown that a high concentration of choline esterase is present at synapses of the central nervous system (Nachmansohn, 1937, 1939b), as well as at the end plates of voluntary muscle (Marnay and Nachmansohn 1938). The enzymatic concentration is high enough to split a considerable amount of acetylcholine (ACh.) during the short refractory period of the effector cells. A preliminary condition is thereby fulfilled for the premise that ACh. might be involved in the transmission process of nerve impulses across central synapses and neuromuscular junctions.

If the high concentration of choline esterase at synapses has a functional significance it might be expected that a relationship exists between the time when brain centers begin to function and the time when the high concentration of enzyme appears. Such a relationship has actually been found in brains of chick embryos and newborn rats, rabbits and guinea pigs (Nachmansohn 1939b). In the brains of chick embryos, which are fairly well developed at hatching, the concentration of enzyme rises markedly during the last 4 days before hatching. In newborn rats and rabbits, which are relatively more undeveloped, the concentration is low and rises to high values during the first 3 weeks after birth, during which time the brain centers develop. In guinea pigs the concentration is high at birth, here again in agreement with the development of the brain. A similar parallelism between function and enzyme concentration has been demonstrated for neuromuscular junctions (Nachmansohn 1939a).

For several reasons it seemed of interest to study this relationship in sheep embryos. Barcroft and Barron (1939) have recently investigated the development of movements in sheep foetuses and have reviewed in connection with their own observations our knowledge of embryonic mammalian movements. Their conclusion is that movements in mammalian embryos are at first mainly local reflex responses. The next step is the domination of the more local reflexes by the reticulo-spinal system. Subsequently the development of the higher centers controlling the movements progresses, until ultimately the whole brain enters into action.

The observations on the unequal rate at which different centers of the central nervous system develop in sheep embryos suggested an investigation of the correlation between the time when the different parts begin to function and the time when the high concentration of choline esterase appears.

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That this concentration rises at an unequal rate in different centers has previously been observed (*l.c.*). However the sheep embryos appeared to be particularly suitable material for two reasons: More data on the development of movements are available in this case than for most other animals (Barcroft and Barron, 1939), and this embryo is rather large in comparison with the other embryos examined and it grows slowly, over a period of nearly 150 days. It is obvious that these conditions greatly facilitate a more detailed study than had been possible in small embryos.

METHODS

The enzymatic concentration has been determined with the manometric method of Barcroft-Warburg. The details are the same as those described previously (Nachmansohn, 1939). The symbols used are:

QCh.E. = mg. acetylcholine hydrolyzed by 100 mg. tissue (fresh weight) in 60 min.

TCh.E. = mg. acetylcholine hydrolyzed by the total organ (fresh weight) in 60 min.

The figures are given for acetylcholine chloride. To obtain the values for the free base, they must multiplied by 0.8.

RESULTS

A. Spinal cord. The 2nd cervical and the 8th dorsal segment have been used. The 8th dorsal segment was chosen because the corresponding roots

Table 1. Changes of concentration of choline esterase in spinal cord during growth of sheep embryos

Age in days→:	60		60		75		76		84	
	W	Q	W	Q	W	Q	W	Q	W	Q
Segment C II	10.0	*11.6*			17.0	*9.1*	30.0	*9.5*	42.0	*10.0*
D VIII	11.0	*12.9*	11.0	*12.3*	29.0	*14.1*	32.5	*16.8*	65.5	*16.0*
Age in days→:	89		93		97		118		136	
	W	Q	W	Q	W	Q	W	Q	W	Q
Segment C II			56.5	*7.2*	42.0	*5.8*	222.0	*5.8*	250.0	*5.6*
D VIII	78.0	*12.8*	60.0	*13.7*	65.5	*8.8*	260.0	*9.3*	202.0	*5.0*

W = weight in mg.
Q = QCh.E.

are chiefly located in the hind limbs. The 2nd cervical ganglion was taken in order to investigate whether the rise of the enzyme concentration during development proceeds in the cephalocaudal direction. The determinations cover the period from the 60th until the 136th day, *i.e.*, near the time of birth. The whole segment without the ganglia has always been taken for the determinations.

The figures of Table 1 show that the concentration of choline esterase in

the 8th dorsal segment is high as early as the 60th day. It continues to rise, reaching a maximum between 75 and 85 days, and then decreases slowly. This decrease is obviously due to medullation of the fibers, since a large number of fibers acquire their myelin sheaths at about this time and the

Table 2. Changes of concentration of choline esterase in different parts of brain of sheep embryos during growth

Age in days:	75		76		84		89	
	W	Q	W	Q	W	Q	W	Q
cerebral cortex	70.2	*1.3*	23.0	*1.3*	30.5	*2.4*		
nuc. caudatus					56.0	*9.2*		
corp. quad. ant.	96.0	*5.1*	114.0	*4.8*	53.5	*6.0*		
corp. quad. post.					19.0	*3.8*		
retina							26.5	*1.6*
cerebellum	215.0	*2.1*	257.0	*2.0*			649	*2.7*
		T		T				T
cerebellum	215.0	*4.6*	257.0	*5.1*			649	*17.7*
Age in days:	97		118		136		138	
	W	Q	W	Q	W	Q	W	Q
cerebral cortex	40.0	2.4			80.0	*3.4*		
nuc. caudatus	91.0	*12.4*	98.0	*22.0*	78.0	*32.6*	102.5	*35.5*
corp. quad. ant.	68.5	*6.5*	197.0	*8.3*	187.0	*15.5*	246.0	*13.5*
corp. quad. post.	30.0	*5.0*	21.0	*3.7*	22.0	*6.8*		
retina			50.0	*6.5*	52.0	*14.2*	33.0	*14.6*
cerebellum			293	*4.8*	149	*13.3*	249	*12.0*
				T		T		T
cerebellum			3260	*156*	4416	*587*	4100	*505*

W = weight in mg. Weight for Q(= QCh.E.) indicates weight of tissue actually taken for experiments; weight for T(= TCh.E.) indicates weight of whole cerebellum.

myelin has a low content of enzyme. The decrease of the average concentration due to the great increase of the number of medullated fibers seems to indicate that there is no further increase of any importance in the concentration of the enzyme in the gray matter. The values of QCh.E. of 12–16 found at the maximum are indeed high if compared with the QCh.E. in the

gray matter of the spinal cord of adult dogs and ox, which are between 6 and 12.

In the 2nd cervical segment the highest value was in an embryo 60 days old. This may indicate that in this segment the maximum is actually reached earlier than in the more caudal segment. But since there are no further data available on such an early stage this cannot be conclusive at the present moment.

In one embryo which was 76 days old esterase was determined in 5 dif-

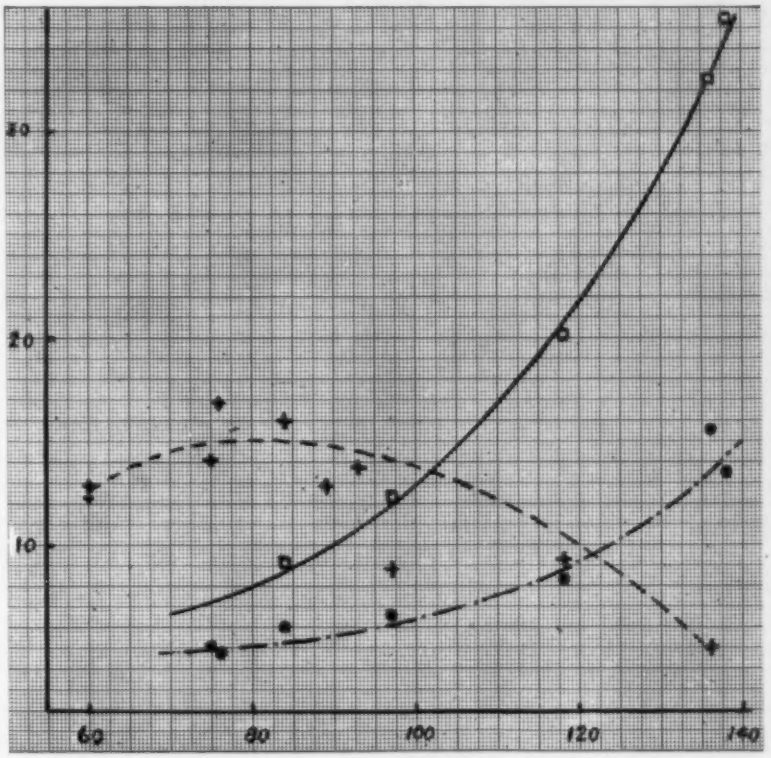

FIG. 1. Changes of choline esterase in brain (nucleus caudatus and corp. quadrigem. anterior) and spinal cord of sheep embryos during growth. Abscissa: days of gestation time. Ordinate: QCh.E. Squares, nucleus caudatus; black dots, corp. quadrigem. anterior; plus signs, 8th dorsal segment of the spinal cord.

ferent segments. The QCh.E. values obtained were 9.5 for the 2nd cervical, 10.0 for the 5th and 6th dorsal, 12.5 for the 7th dorsal, 16.8 for the 8th dorsal and 12.0 for the 3rd lumbar segment. The weights were 30.0, 23.5, 37.5, 32.5 and 40.0 mg. respectively. It appears from these figures that the highest concentration among the segments examined exists in the 8th dorsal segment. This may be related to the fact that the number of cell bodies and synapses in this segment is higher than in the others.

B. Brain. The following parts have been examined: cerebral cortex, nucleus caudatus, corpora quadrigemina ant. and post., retina, and cerebellum. The age varied between 75 and 138 days. The figures of Table 2 show that, in contrast to the development in the spinal cord, the concentration of the enzyme is low in all these brain centers at the age of 75 days and then rises continuously and steeply. In the cerebral cortex the increase is relatively small compared with that in other parts.

It must be kept in mind that, unlike the segments of the spinal cord as used in the experiments, the parts of the brain used contain mainly gray matter. There is, therefore, no opposed effect on the QCh.E. from white

Table 3. Changes of concentration of choline esterase in some striated muscles of sheep embryos during growth

Age in days:	75		76		84		89		97	
	W	Q	W	Q	W	Q	W	Q	W	Q
leg muscle	232	*1.7*					326	*2.6*	149	*2.5*
intercostal muscle			71	*3.9*					275	*4.2*
extrinsic eye muscle			44	*8.6*	49	*9.5*			57	*9.3*

Age in days:	118		132		136		138	
	W	Q	W	Q	W	Q	W	Q
leg muscle	664	*2.1*			239	*1.2*		
intercostal muscle	270	*2.3*	370	*2.2*			502	*2.1*
extrinsic eye muscle	60	*6.6*	114	*7.8*	147	*12.0*		

W = weight actually used in mg.
Q = QCh.E.

matter to such an extent as in the spinal cord; but in spite of this reservation the difference between brain and spinal cord is obvious and striking (see Fig. 1).

The increase in total enzyme activity is even larger than the figures of the QCh.E. indicate, because the mass of the brain increases considerably during the same period. The total increase is demonstrated by the TCh.E. calculated for the cerebellum, as this part is the most suitable for such estimation. The TCh.E. of cerebellum rises from 5 at 75 days to over 500 before birth.

The cerebral cortex begins to develop considerably from about the 80th day on. It may be that the relatively small increase of the QCh.E. of the cerebral cortex is due to the enormous increase of the mass, whereby the increase in concentration is less apparent.

C. Muscle. The rapid development of muscle of chick embryos examined

in previous experiments covers only a few weeks. Moreover in these small muscles many nervous elements develop in a relatively small space. At the period at which end plates appear the enzyme concentration is rapidly rising. But it is difficult to ascertain in such a complex formation how far this rise is linked with the appearance of end plates.

It has been observed (Dickson 1940) that in intercostal muscles of sheep embryos motor end plates are not yet present at 100 days and have a simple form even at 137 days. These muscles and leg and extrinsic eye muscle have been examined. The figures of Table 3 show that around the period from 80–100 days the QCh.E. of leg and intercostal muscles reach the highest values. Muscle fibers have a low content of enzyme. As the relative volume of fibers becomes more important in later periods of development, the relatively high values of QCh.E. in the early period indicate that at this time a high concentration of enzyme already exists in the region of nerve endings. Recent investigations (Couteaux and Nachmansohn, 1940) suggest that a high concentration of choline esterase exists both inside and outside nerve endings at end plates. Whether the enzyme at an early stage is also localized both in and around nerve endings cannot yet be decided.

It is known that extrinsic eye muscles contain a large number of end plates. The concentration of enzyme in these muscles is particularly high at an early stage. But the number of experiments is not sufficient to permit an interpretation of the changes during growth.

Discussion

The chief result of the experiments described is evidence that the high concentration of choline esterase appears in different parts of the central nervous system of sheep foetuses at different periods of embryonic development. The concentration is high in the spinal cord at an early stage (60–80th day), it is low at that time in brain centers. In these centers it rises rapidly during the last weeks before birth. This is in agreement with the development of the activity of these centers in the animals as observed by Barcroft and Barron (1939) on the development of movements. It brings new evidence of the close relationship between the time when the high concentration of enzyme appears and the time when brain centers begin to function, indicating the physiological significance of the enzyme.

Several details discussed in the text remain unexplained. *E.g.*, the work does not cover the earlier period before the 60th day, which would be of special interest for the question of a development in the cephalocaudal direction. But the experiments demonstrate the suitability of the material for such investigations.

The observation that the enzyme is highly concentrated at the region of nerve endings in muscle at an early age, long before the formation of end plates, apparently indicates that the concentration is more closely related to the function than to the histological formation.

Summary

1. Choline esterase is present at a high concentration in the spinal cord of sheep foetuses at an early age of gestation (60–80th day). It is low at that time in brain centers where it rises rapidly during the last weeks before birth. The experiments emphasize the close relationship between function of brain centers and the enzyme studied.

2. In striated muscle the enzyme is also highly concentrated at the region of nerve endings at an early age long before end plates appear.

3. A remarkably high concentration is found in extrinsic eye muscles, this too at an early period.

This work was undertaken following a suggestion from Sir Joseph Barcroft and Dr. D. H. Barron, to whom I am greatly indebted for advice and help. The experiments were carried out in the Sir William Dunn Institute at Cambridge. It is a great pleasure to thank Sir Frederick Gowland Hopkins for hospitality. His stimulating interest in the work was a great encouragement.

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CENTRAL COURSE OF "RECURRENT" SENSORY DISCHARGES*

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Course of "Recurrent" Sensory Discharges

The first evidence, obtained by oscillographic methods, that impulses leave the spinal cord via the dorsal roots was presented by Matthews in 1934. In this preliminary publication Matthews identified three types of impulse discharges: (i). "sensory like," (ii. "motor like," and (iii), those conducted in small fibres.

The "sensory like" discharges were investigated further (Barron and Matthews, 1935a) in conjunction with the peculiar phenomena of intermittent conduction, already recognized by Matthews (1934). These impulse discharges, except for intermittent interruptions in the impulse series, were identical with impulse discharges recorded from sensory nerves. They entered at one fibre and after traveling some distance in the posterior columns emerged again by another to travel toward the periphery. This central pathway and its properties were studied physiologically after the entering and emergent rootlets were found for an individual sensory discharge. The physiological properties of this pathway were such that it appeared to be a single fibre; for the conduction time was that of a continuous fibre, and conduction took place in either direction at the same rate.

On the basis of these physiological observations the nature of the pathway traveled by these sensory-like discharges was postulated (Fig. 2a). The impulses were assumed to travel in via a normal sensory fibre (b) to ascend the cord and to leave it again via a collateral of that portion of the fibre directed toward the terminal nucleus at the end of the medulla.

As these collaterals presumably had no cell body in the ganglion of the root via which they left the cord, they ought to have remained as intact fibres in the central end of that root after the connection with the ganglion was destroyed by cutting the posterior root. Posterior rootlets were sectioned in cats in an effort to test the agreement between the physiological evidence and the structural hypothesis. Intact fibres were found in the rootlets and the anatomical evidence appeared to be in agreement with the physiological evidence (Barron and Matthews, 1935b).

This anatomical evidence has been challenged repeatedly. The careful degeneration experiments of Tower (1940) and of Hinsey (1936) and their collaborators, who find no intact fibres in the central portion of the root nor

* The histological observations were completed and the manuscript was prepared while the author enjoyed a Sterling Fellowship in the Department of Zoology, Yale University. It is a pleasure to acknowledge my indebtedness to Professor L. L. Woodruff and his staff for their hospitality and assistance.

degenerated fibres in the distal portion after section between the ganglion and the cord, cast serious doubt upon the existence of fibres of the type postulated. The question continued to recur—what is the nature of the pathway traveled by those impulses? The following experiments were undertaken during 1935 and 1936 to reinvestigate the nature of the path.

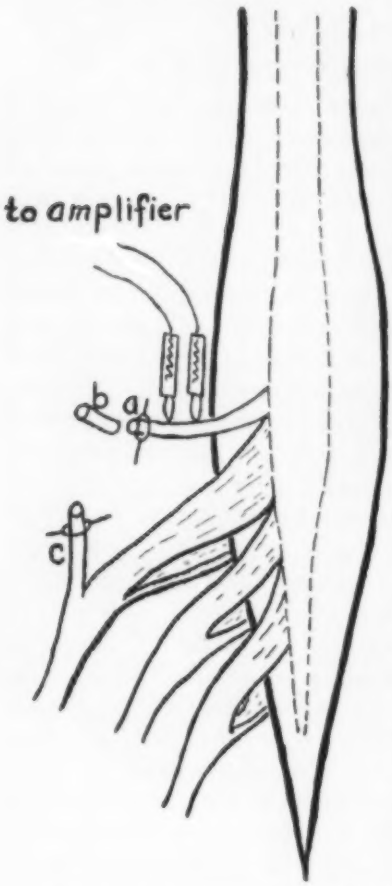

FIG. 1. A diagram illustrating the experiments designed to identify rootlets conducting recurrent discharges, and to obtain histological samples of them before and after degeneration. *a*. The central end of rootlet from which discharge was recorded before and after degeneration. *b*. The section removed at first experiment. *c*. The peripheral portion studied histologically after degeneration.

MATERIALS AND METHODS

For experimental animals rats were used instead of cats as in the original experiments. The same "recurrent" sensory discharges occurred, and the central pathway they traveled had the same properties that were described for the cat. Rats were chosen principally because they could be operated upon without danger of infection if reasonable precautions were taken. This same resistance to infection made it possible to operate upon an animal and record the action potentials in the rootlets without elaborate technical arrangements.

In practice the individual rats were anesthetized with sodium amytal. A laminectomy was performed and several tiny rootlets prepared for recording. The fibre bundles were selected from the long lumbar roots and raised free up to the entry into the cord. The distal portion was freed out as far as was conveniently possible. The rootlet was then sectioned so that a small length was taken out midway between the ganglion and the cord (Fig. 1). A colored silk thread was then tied on the tip of the central portion (*a*) and one of the same color on the peripheral portion (*c*). The sector removed (*b*) was fixed at once in 1 per cent osmic acid and labeled for identification. In a single animal usually 5 rootlets were prepared in the same way. The rat was then placed in a warm box and arrangements completed to lead from the central ends of the cut rootlets through amplifiers to a loud speaker or oscillograph. If active fibres conducting sensory-like discharges toward the periphery were found in these rootlets, a photographic record was made of the discharge and an estimate made of the number of fibres. Such a record was kept for each individual rootlet. The rootlets were then placed alongside the cord or tucked down among the roots for protection. The skin was closed over the cord with michel clips after it had been bathed in a weak solution of lysol. At intervals varying between 3 and 28 days after the operation these rats were reexamined. The cord was reexposed and the individual rootlets were lifted upon the recording electrodes. First the peripheral part was examined and then the central portion of the corresponding rootlet. Where degeneration had been allowed to proceed longer than 21 days the central portion was often so *lacking* in strength that it was gotten on the electrodes only with difficulty. After the observations had been made with the amplifier for action currents, the two portions of the rootlet were removed and fixed, usually in 1 per cent osmic. In some cases the central portion was fixed in osmic acid and the peripheral portion prepared in potas-

sium dichromate for the Marchi technique. These portions of the rootlet together with those taken at the first operation were embedded in paraffin and sectioned serially at 10μ.

Results

Following this procedure, observations were made in over one hundred individual rootlets that were known at the first operation to have fibres conducting sensory-like discharges toward the periphery. Some of these could not be used for histological studies for the original piece removed and fixed at the operation, when studied histologically, had fibres already present in small numbers. In 87 rootlets, however, action currents were recorded in the central portions and the histological control was free from evidence of degenerating medullated fibres. In not one of the peripheral portions of these rootlets was there any evidence of degenerating fibres either after the osmic acid or the Marchi method. As a counterpart of this observation, action potentials could not be recorded from the central portion three days after it was sectioned, though it had carried recurrent sensory discharges previously. As a control against damage not directly associated with the resection, other rootlets were picked up and records made from their central ends after resection.

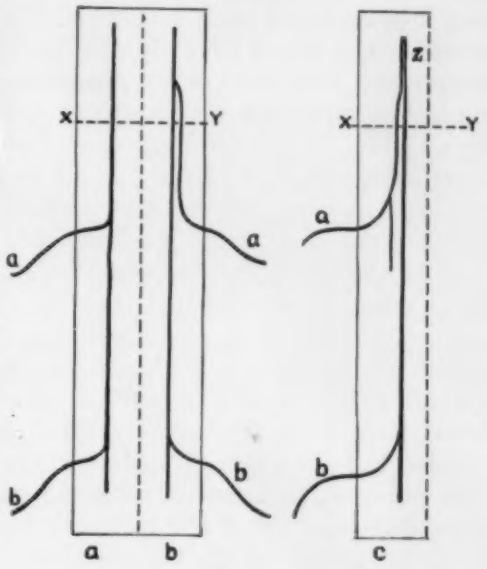

FIG. 2. Diagrams of the spinal cord illustrating the possible central paths taken by recurrent sensory discharges that are interrupted by lesions (x – y) in the cord not placed between the entering (b) and emergent (a) rootlets. (a) Section at x – y would not interrupt the conduction between a and b. (b) A possible modification of (a) in which lesion at x – y would interrupt conduction between a and b. (c) If impulse transmission took place between fibres (a) and (b) at point z lesion x – y would interrupt it.

These results are clearly incompatible with the existence of recurrent collateral fibres of the type postulated as a result of experiments on cats (Barron and Matthews, 1935). Even if they existed in small numbers the chances of detecting them ought to be extremely high, by degeneration methods in the periphery or by recording from the central end, for the majority of the rootlets contained less than 250 medullated fibres.

In addition a second bit of evidence throwing doubt upon the original pathway postulated was discovered while testing the central course of the "sensory-like" discharges in rats. In a number of animals in which the centrifugal and centripetal rootlets had been identified it was possible to destroy the central pathway, not by cutting across the dorsal columns between

the rootlets, but either above or below them (Diagram, Fig. 2). Unless the central portions of the dorsal root fibres have quite another course than that usually ascribed to them such as postulated in Fig. 2b, the result of this experiment can only mean that there are 2 fibres concerned in this central pathway and that impulse transmission is, under the conditions of the experiment, taking place between them in a one to one ratio without appreciable delay. From the earlier evidence on the cat and the rat this process might be expected to be reversible. A similar artificial synaptic relationship between the fibres of peripheral nerves in crabs has been described by Jasper and Monnier (1938). Assuming the existence of such a synapse the central pathway for the recurrent sensory discharges might be illustrated by *c* in Fig. 2. The discharge might enter via *b* and ascent to Z where the close approximation of the fibres would enable *b* to excite *a*. The impulses would then reach the periphery again via *a*. A cut through the posterior columns cut *x*—*y* would interrupt this pathway.

The phrase "under the conditions of the experiment" might be stressed for it must be remembered that the cord has been exposed and the dura opened. Under these conditions the insulation between individual fibres might be decreased or their accomodation mechanisms disturbed after the manner in which similar exposure affects the terminal portions of the posterior root fibres (Barron and Matthews, 1938). Moreover, it should be pointed out that, though these recurrent sensory discharges may be traced into and recorded from the sensory nerves to the skin of a rat after laminectomy and exposure of the cord, this has not been possible in a rat with the cord unexposed but simply anesthetized.

In conclusion, therefore, the observations presented here do not support the hypothesis that the "recurrent sensory-like" discharges are conducted through the spinal cord and out again toward the periphery in a single continuous fibre. They indicate that at least two fibres may be involved and emphasise the need for a reinvestigation of the physiological relations of their central pathway.

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INTERCORTICAL CONNECTIONS OF CORPUS CALLOSUM AS INDICATED BY EVOKED POTENTIALS

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INTRODUCTION

THE INTERCORTICAL connections of the corpus callosum have been investigated by a number of different workers using degeneration methods (Mettler, 1932, 1935; Mingazzini, 1922; van Valkenberg, 1913). The limitations of such methods are well known. Within recent years a much more convenient and precise method of studying fiber connections has been introduced, namely, the oscillographic method, in which a stimulus is applied to the afferent nerve ending and the corresponding action potential recorded from the regions which receive these fibers. The present work is an investigation of the intercortical connections of the corpus callosum by this method.

EXPERIMENTAL PROCEDURE

Twenty cats and six monkeys under barbiturate anesthesia were used in the present investigation. A rather extensive exposure of both cerebral hemispheres was made, and the dura was removed. The animals were kept in a room having a relative humidity of about 80 per cent and a temperature of about 30°C.; under these conditions the cortex remained in good condition for many hours. Single electrical shocks were applied to the surface of the pia by means of bipolar silver-silver chloride electrodes about 1 mm. apart, and the pick-up electrode consisted of a small chlorided silver wire lightly resting on the pial surface. The recording system is described in another paper (Curtis, 1940b); it consisted of an amplifier and cathode ray oscillograph.

RESULTS

A single electrical shock applied to the pial surface of one hemisphere will, in general, evoke a potential in the opposite hemisphere at one or more points (Curtis and Bard, 1939). A record of a typical potential is reproduced in Fig. 1. In general it is diphasic, but at times either the positive or negative phase may be so small as to make it appear to be monophasic. The height may vary from the limit of resolution (about 4 μV) up to several millivolts. Evidence of very discrete localization may be obtained by this method. In some cases concentric electrodes, of which the outer one was only 0.25 mm. in diameter, were used for stimulation. With this arrangement it was frequently found that a point exhibiting a large response may be only 1 mm. away from a point which shows no measurable potential. Because of this fact bipolar electrodes 1 mm. apart giving a somewhat diffuse stimulation were usually used.

There can be no doubt that these responses are mediated by the corpus callosum, since they are completely abolished by section of this structure at

the mid-line. When the stimulus is repeated about once a second the callosal potential produces a standing pattern on the face of the oscillograph. Under these conditions any changes which may take place in the responses can easily be observed. If the cerebral hemispheres are separated slightly at the mid-line, a stimulating electrode can be placed directly on the callosum. Since stimulation here gives exactly the same type of potential as is observed when the appropriate point in the opposite hemisphere is stimulated, it is a procedure which may be employed to determine the path of the fibers in the callosum. When the region in the callosum containing the fibers connecting any two points has thus been determined, a small cut there immediately abolishes the electrical response to stimulation of the related contralateral point, but may not affect potentials at neighboring points.

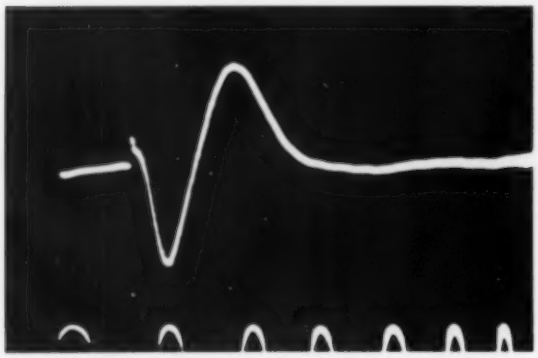

FIG. 1. Typical potential wave recorded from the surface of the pia on stimulation of the symmetrical point of the opposite hemisphere. Middle suprasylvian gyrus of cat. An upward deflection indicates a surface negative potential. Time marks 60 cycles.

The largest and most readily detected potentials are those obtained when stimulating and recording electrodes are placed on symmetrically situated points of the two cortices. Thus it is possible to determine the relative abundance of callosal connections between symmetrical points in different

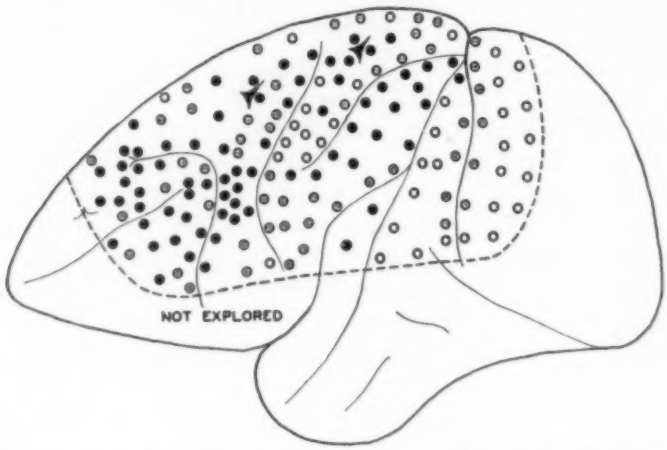

FIG. 2. Lateral view of left cerebral cortex of a monkey. Marks indicate the relative magnitudes of potentials evoked at different points by stimulation of the symmetrical points of the opposite cortex. Results of an experiment on one animal. ● Large potentials; ⊙ medium potentials; ○ small or no potentials.

regions by systematically exploring the cortex with a constant stimulus, always keeping stimulating and pick-up electrodes on symmetrically situated points and maintaining constant amplification. The height of the potential may then be taken as a rough measure of the extent of callosal association between the two points. The results of such an experiment on a monkey are shown in Fig. 2, where solid circles indicate points which gave large potentials, dotted circles medium potentials, and open circles weak or no potentials. Figure 3 is a composite map drawn from results obtained in about 15 experiments on cats. It will be seen from these figures that the distribution of callosal fibers between different cytoarchitectonic areas, or even between different parts of the same area is by no means uniform. Whereas the map of Fig. 2 shows the results obtained in the case of only one animal, each of the experiments on monkeys showed the same general pattern of distribution. The absolute magnitude of the potentials recorded from different monkeys varied considerably, but the relative heights of these potentials at different points were fairly uniform. The same is true of the cat, but the absolute magnitude of the potentials in the cat is much less than in the monkey, and in any individual cat there may be a considerable fraction of the exposed cortex from which it is impossible to obtain measurable potentials. However, by the use of a number of cats it has been possible to show that there is no part of the cortex which was explored which does not give these potentials at symmetrical points. In the case of the monkeys, the same is true with the exception of the striate cortex, area 17 of Brodmann; it has not been possible to obtain any indication of a potential from any part of this area on stimulating a symmetrical point.

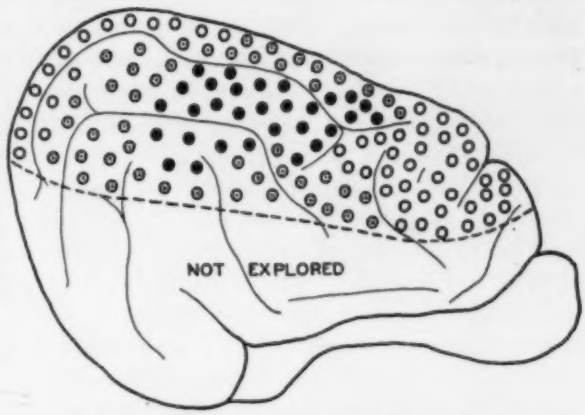

FIG. 3. Lateral view of right cerebral cortex of a cat. Marks indicate the relative magnitudes of potentials evoked at different points by stimulation of the symmetrical points of the opposite cortex. Summary of results obtained in fifteen experiments. ● Large potentials; ⊙ medium potentials; ○ small or no potentials.

It has been found (Curtis, 1940a) that the application of a convulsant drug such as strychnine or picrotoxin to the surface of the pia under the recording electrode will in general enormously enhance the recorded potential. This fact can often be used as a means of amplifying a potential which was previously difficult or impossible to record with certainty, but sometimes the enhancement occurs only when the potential is initially quite large. The strychnine effect has been used to check some of the results described above. It is apparent that the absence of potentials from area 17 of

the monkey does not necessarily indicate that there are no connections, but it does give presumptive evidence that if present, they must be rather weak.

In addition to the potentials observed when stimulating and pick-up electrodes are situated at symmetrical points, potentials are often observed in quite different regions. This effect is much more pronounced in the monkey than in the cat. Thus in order to determine all the intercortical connections of the callosum it would be necessary to stimulate systematically each point of one cerebral cortex and for each position of the stimulating electrodes to explore systematically the entire opposite hemisphere with the pick-up electrodes. This has been done for only a relatively few selected points, and the results of one such experiment are shown in Fig. 4. Here the

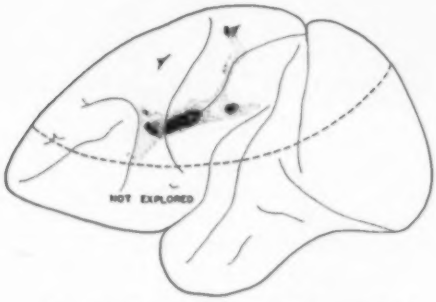

FIG. 4. Lateral view of left cerebral cortex of a monkey in which are indicated the relative magnitudes of potentials obtained as a result of stimulating the point on the right cortex symmetrical to the one marked *X*. The degree of shading indicates the relative magnitudes of the potentials obtained in this experiment.

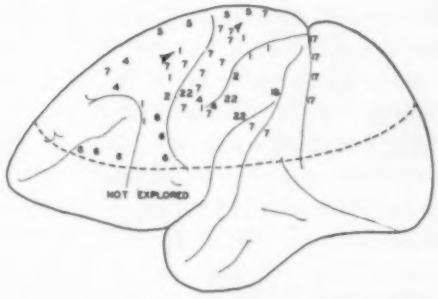

FIG. 5. Lateral view of left cerebral cortex of a monkey. The numbers indicate areas of Brodmann which send callosal fibers to the region containing the number.

stimulating electrodes were on the hemisphere opposite the one shown and at a point symmetrical to the one marked *X*. The degree of shading indicates the relative heights of the potentials. It is obvious that the problem of representing such data from a number of experiments is a difficult one. However, this has been attempted in the map of Fig. 5, which only indicates projections to regions other than the cytoarchitectonic area within which the stimulus was applied. The numbers refer to areas of Brodmann (1909) which send callosal impulses to the region where the number is situated. It should be pointed out that this map by no means implies that all points in an area project to the points indicated, but when any region, however small, was found to project to another cytoarchitectonic area, it was indicated. These regions were sometimes only one or two square mm. in size. Since by far the most numerous connections are to corresponding cytoarchitectonic areas, the map of Fig. 5 is a gross over-simplification of an exceedingly complex system of interconnections.

The question immediately arises whether these inter-areal connections

are by means of direct fibers in the callosum or depend on intracortical spread of activity. All evidence at the present time points to the former alternative. In the first place, no difference can be detected in the latency of the response at various places, and in the region between two points giving relatively large potentials there may be no measurable response. Furthermore when stimulation on one side evokes two large potentials, one at the contralateral symmetrical point, *A*, and another at a point, *B*, some distance from *A*, the isolation of *B* by cutting through the cortex around it, does not affect either potential. In a general way fibers joining any two points take the shortest path in the callosum between these points. In one experiment on a monkey a point in the anterior part of area 6 gave a good potential in response to stimulation of a point in the contralateral area 7. Two fairly large sagittal cuts were then made in the callosum at the midline, one medial to area 7 and one medial to area 6, leaving only a small bridge of intact callosal tissue on a line between stimulating and pick-up electrodes. The recorded potential was unaffected by this procedure, but it was completely abolished when the remaining part of the callosum was cut. This evidence points rather strongly to the existence of direct callosal connections between all points indicated in Fig. 5. When two or more points which are quite close together exhibit large potentials in response to stimulation of a contralateral point, it is difficult to determine whether the multiple response is due to separate callosal fibers to each point, or to intracortical spread from one point to another. Employment of the same procedure as outlined above indicates that, as in the case of widely separated points, there are separate fiber connections.

Discussion

The evidence presented here is in good agreement with previous work. However, the lesions which have been made in attempts to study this problem by following degeneration were so large relative to the area stimulated in these experiments, and the consequent degeneration so extensive, that comparisons are difficult. Mettler (1932, 1935) found the greatest degeneration in regions symmetrical to the lesions, and this led him to a generalization which is abundantly confirmed in these experiments. The only significant point of difference between the results of the present work and those of Mettler involves the question of callosal connections between the striate areas of the monkey. Mettler (1935a) reported the occurrence of degeneration of callosal projections from area 17 of one cortex to the corresponding region of the other hemisphere, but the results of the present study are entirely negative in this respect. Other investigators have denied the presence of callosal connections between these areas (van Valkenberg, 1913; Mingazzini, 1922). This point is of interest in reference to theories of binocular vision. It was pointed out above, and should be emphasized here, that the absence of potentials does not necessarily mean that there are no connections. It would, however, seem fairly safe to conclude that if such callosal

connections exist, they must differ markedly from those which relate other symmetrical areas. There are abundant connections between the visual association areas, and also between the visual motor areas of the two hemispheres. It is interesting to note (Fig. 3) that the experiments on cats revealed the existence of fairly strong callosal connections between the two striate areas. This is in agreement with the results of Poliak's (1927) anatomical studies. It is possible that in the cat the visual projection and visual association areas are not as differentiated anatomically as they are in the monkey.

The maps showing the relative strengths of callosal potentials at symmetrical points (Fig. 2 and 3) are interesting in that there seems to be no consistent correlation between the function of an area and the strength of the symmetrical callosal connections. Again it should be emphasized that the size of the potential may or may not be a true index of the strength of the callosal connections. The position of the majority of the endings in the cortex would undoubtedly affect the size of the potential as much as the density of the callosal fibers. Micro-electrode studies in the cat (Curtis, 1940b) seem to indicate that the positions of the endings of callosal afferents within the cortex are approximately the same in all areas investigated, but relatively few areas have been explored in this way in the cat, and none in the monkey.

The map of Fig. 5 shows that there seems to be no particular relation between the function of an area and its callosal projections to other areas. For example it might be expected that there would be abundant callosal connections between area 4 and area 6, but such is not the case. Of the cortical regions explored, area 7 appears to have the most abundant callosal projections to other areas.

The question arises of course as to how much of the observed potential is due to antidromic stimulation. Stimulation of a given region of one hemisphere may evoke a potential in a totally different region of the opposite hemisphere but if stimulating and pick-up electrodes are reversed, no potential can be observed. For this and other reasons it has been concluded (Curtis, 1940b) that antidromic impulses play a very minor role in the production of the potential as recorded at the surface of the pia.

It is interesting to speculate as to what these results may indicate concerning the function of the corpus callosum. The first indication is that the chief connections between the hemispheres are to symmetrical points and that other connections are probably of relatively minor importance. A clew to its function may lie in the fact that areas of the cortex which control the motor movements of muscles which usually function synchronously on the two sides of the body have abundant callosal connections. For example, the motor face, head, and trunk areas appear to have stronger connections in general than the arm, leg, or hand areas.

Summary

In monkeys and cats under barbiturate anesthesia single electrical shocks were applied to the cortex of one hemisphere and the other cortex explored for evoked potentials. The only regions not studied were those which cannot readily be exposed by removal of the calvarium. In general it may be said that localized stimulation of one cortex gives rise to distinct evoked potentials in one or more specific places on the other cortex. The magnitude of the response is quite variable; it may be as large as several millivolts. In general the waves are diphasic and sometimes have a duration as long as 100 msec.

The largest and most readily detected potentials are those obtained when the stimulating and recording electrodes are placed on symmetrically situated points of the two cortices. In the cats studied all regions yielded potentials from symmetrical contralateral stimulation. With the exception of the operculum of the occipital lobe (area 17) the same was true of the monkeys. Localized stimulation within certain areas may evoke potentials over a considerable portion of the corresponding contralateral area and sometimes in other contralateral areas. The responses obtained under the conditions of these experiments are mediated by direct callosal fibers and are not dependent upon intracortical spread of activity. In general the evoked potentials are quite sharply localized. They are fairly reproducible from animal to animal.

These effects are completely abolished by section of the corpus callosum.

The author wishes to express his appreciation to Dr. Philip Bard for his advice in all parts of this work.

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AN ANALYSIS OF CORTICAL POTENTIALS MEDIATED BY THE CORPUS CALLOSUM

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INTRODUCTION

IN ATTEMPTING to analyze the functions of the cerebral cortex the recording of electrical potentials generated by the cortex has proved to be very valuable. For the most part such studies have been carried out by placing electrodes either on the skull or on the exposed surface of the pia and recording the spontaneous activity. Analyses of these potential changes have proved to be difficult for the reason that any or all of the elements of the entire central nervous system may be contributing directly or indirectly to the activity. In many respects a much more satisfactory method is that of studying the potential changes of the cortex which result from stimulating afferent fibres or some sense organ. Such studies have been carried out by a number of investigators on various cortical afferent systems. Perhaps the simplest anatomical picture of a corticipetal system is presented by the intercortical fibers of the corpus callosum.

The cell bodies of the axons which form the callosum lie in layers III, V, and VI of the cortex (Pines and Maiman, 1939). On entering the cortex of the opposite hemisphere the callosal fibers ramify profusely in layers IV to II and end in layer I (Kölliker, 1896; Lorente de Nó, 1922, 1938). If one cerebral hemisphere is stimulated with single electrical shocks (Curtis and Bard, 1939; Curtis, 1940b) potentials will be evoked at one or more points on the surface of the opposite hemisphere, and these potentials are mediated by the corpus callosum.

Whenever a cortical potential is obtained as a result of afferent stimulation, one has direct evidence that there is a neural connection between the nerve being stimulated and that point on the cortex. However, this gives very little evidence concerning the mechanism whereby this potential is produced. A number of investigators (Bishop and O'Leary, 1936; Lorente de Nó, 1939; Renshaw, Forbes and Morison, 1940), by inserting microelectrodes into various parts of the central nervous system, have recorded potentials of discrete local origin. An analysis of such data has furnished much valuable information concerning the origin and function of various neuron systems. The present work is an attempt to make such an analysis of the callosal system.

PROCEDURE

Twenty-two cats, under barbiturate anesthesia, were used in these experiments. The calvarium and dura were removed over both cerebral hemispheres. The head of the animal was rigidly fixed in a holder to which various electrodes were attached in such a way that

any one of them could be placed on any part of the exposed cortex and one of them inserted to any desired depth. Single electrical shocks were applied to the pial surface through an isolation transformer by means of silver-silver chloride bipolar electrodes about 1 mm. apart.

The micro-electrodes which were used for recording consisted of glass micropipets, drawn to an inside diameter of about 50μ and filled with a gel of agar in Ringer's solution, into which a chlorided silver wire dipped. Some of the electrodes were bipolar, consisting of two such capillaries fused together, one of which was broken off about 200μ shorter than the other. The advantages, applications, and limitations of such electrodes have recently been discussed thoroughly by Renshaw, Forbes and Morison (1940) and will not be repeated here. Suffice it to say that with these electrodes it is possible to obtain responses of very local origin and that both monopolar and bipolar recording should ultimately lead to the same conclusions. All conclusions reached in this work were based on examinations of records taken by both types of electrodes.

The electrode holder for the micropipets was so arranged that they could be inserted at any angle and the depth of insertion accurately measured by means of a scale attached to the slider of the holder. The position of the electrode in the brain was also determined by subsequent histological examination of serial sections. A reference point for the depth measurements was established at the end of each insertion by placing beside the pipet a fine glass rod which was made lightly adherent to it by means of a small amount of mineral oil. On inserting the pipet the rod followed only as far as the surface of the pia. On removing the pipet the depth of insertion of the needle for that particular setting of the scale of the electrode holder was given by the distance between the end of the rod and the end of the needle. From measurements made on serial sections of the brain it was thus possible to locate, in terms of each scale setting, the position of the electrode in relation to the various cortical layers and the underlying white. It was determined that these measurements were accurate to about 100μ. It should be emphasized that the electrodes were very small and had very sharp points. On piercing the pia they caused only a slight momentary indentation. Thereafter the electrode could be raised or lowered without causing an appreciable movement of the cortex. For these reasons the depth measurements made by the method indicated above proved to be more reliable and convenient than any of several other methods which were tried in attempts to mark the position of the electrode in the cortex for subsequent histological identification. The electrodes were so small that inserting them caused no measurable change in the callosal potential recorded separately at the surface. The electrode could be raised or lowered as often as desired without changing the potential as recorded from the micropipet at a particular scale setting even when a change of 100μ caused a radical change in the potential picture.

For recording the potentials a direct-coupled amplifier with common mode degeneration was used in conjunction with a cathode ray oscillograph. A condenser was usually inserted between the second and third stages of the amplifier to eliminate drifts. Whenever there was any doubt about the true wave form, this condenser was switched out and the potential recorded with the direct coupled amplifier. The micro-electrodes had a resistance of several megohms. Since this resistance, in conjunction with the capacity of the leads from the amplifier to the preparation, is an arrangement which would shunt out any very rapid potential changes occurring in the neighborhood of the electrodes, this source of error was eliminated by mounting an impedance changer on the carriage of the electrode holder next to the micropipet.

Changes in the size and shape of the callosal potentials recorded from the surface of the pia occurred from time to time. Therefore a separate electrode was placed on the surface of the pia over the region being explored in depth with the micropipet. It was connected to a separate amplifier and oscillograph. If the surface potential changed during a series of observations made with the micro-electrodes, the series was either repeated or discarded.

Results

A normal callosal potential, as recorded from macro-electrodes on the surface of the pia, is shown in the uppermost record of Fig. 1. There is, of course, considerable variation in the size and shape of such potentials. In general, they consist of an initial surface positive component followed by a surface

negative component. The entire wave may last as long as 100 msec. The two components are separate and distinct. That such is the case is shown by (i) their different sites of origin as revealed by micro-electrodes and (ii) the differential action of drugs. If a small quantity of a narcotic such as nembutal or cocaine is placed on the pia over a small area receiving callosal impulses, the negative component of the potential is obliterated, but the positive remains unchanged (Curtis, 1940a). On the other hand, if a small amount of a convulsant drug such as strychnine, picrotoxin, metrazol, etc. is added in the same way, and enormous enhancement of the negative component occurs (Bartley, O'Leary and Bishop, 1937). These phenomena are shown by the records of Fig. 1, all of which were taken from the same point on the pia. The first is the normal, the second was obtained after the local application of nembutal, and the third after application of strychnine. Before the record showing the effect of the strychnine was taken, the effect of the nembutal had completely worn off and the wave shape had returned to normal. Thus it is possible, by means of drugs to separate the two components and to analyze each separately.

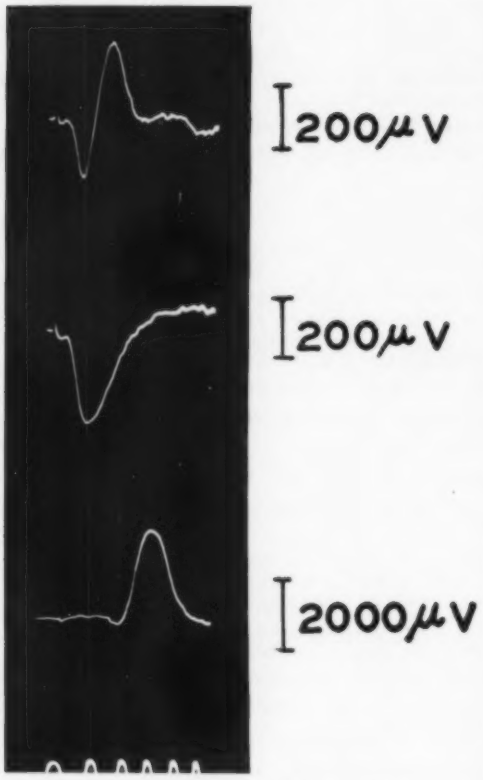

FIG. 1. Potentials recorded with a macro-electrode on the surface of the middle suprasylvian gyrus in response to contralateral cortical stimulation. The upper record is a typical normal wave; the center record was taken at the same point after the local application of 6.5 per cent nembutal at the recording electrode; and the lower record after application of 1.0 per cent strychnine sulfate. Upward deflection indicates a surface negative potential. Time marks, 60 cycles.

No fast axon-like spike potentials such as those recorded by Renshaw, Forbes and Morison (1940) from micro-electrodes in the hippocampus were ever obtained from either the cortex or the callosal fibers leading to the cortex. Failure to observe such potentials during numerous experiments means either that the observer was extremely unlucky or that the elements contributing to the potentials are numerous and small in comparison to the size of the electrodes.

Considering first the initial positive wave, Fig. 2 shows records taken with a micropipet at various depths below the surface of the pia after the local application of nembutal. Subsequent histological examination showed

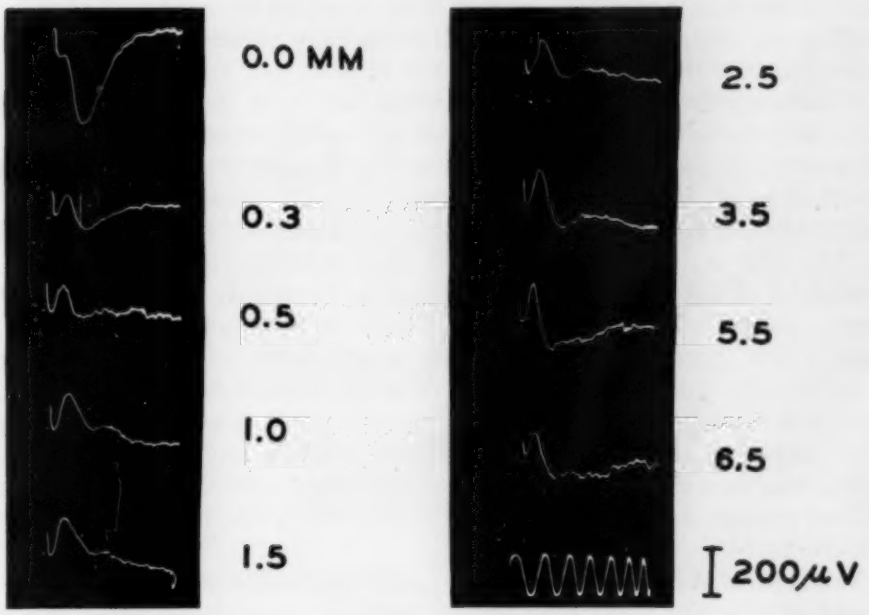

FIG. 2. Potentials recorded with a unipolar micro-electrode from various depths below the surface of the middle suprasylvian gyrus in response to contralateral cortical stimulation. All records were taken after the local application of 6.5 per cent nembutal at the site of entry of the recording electrode. An upward deflection indicates that the active electrode was negative with respect to the indifferent electrode. Time record, 60 cycles.

that the electrode had gone straight down into the white matter of the gyrus as in the section shown in Fig. 3. At this point the cortex is 2.0 mm thick. When electrodes were inserted in the gray matter of the gyrus just medial and lateral to the needle tract from which these records were taken no activity was recorded; it is therefore clear that they were not simply due to the presence of large potentials originating at a distance. It will be noticed from the records of Fig. 2 that when the electrode is completely in the white matter, the wave is predominantly negative. As the electrode leaves the white matter and enters the gray there is no discontinuity in the records until a point about 0.5 mm.

FIG. 3. Frontal section of middle suprasylvian gyrus showing a micro-electrode track.

from the surface is reached. Here the wave starts to reverse, but this reversal is not complete until the electrode is only about 0.1 mm. below the surface, *i.e.*, in the upper part of layer I.

These records show that no particular cell layer is responsible for the production of the initial positive wave; one would expect a marked change in the record as the electrode went through this layer, if such existed. On the the other hand, it is possible to interpret these records as being due to summated axon spikes. This problem has been treated theoretically by Wilson, Macleod and Barker (1933) and the applications of their theory to phenomena in the central nervous system have recently been discussed by Lorente de Nó (1939). They showed that in a volume conductor (*e.g.*, Ringer's fluid), records taken between an indifferent electrode and one in the center of a fiber tract consisting of similar fibers discharging synchronously will show a triphasic wave. The first phase is positive and small, the second negative and large, and the third positive and small. It may be pointed out that if the fibers are firing somewhat asynchronously, the first and last phases, being small, would be obscured, leaving an almost pure negative wave.

At the present time there is no adequate theoretical treatment which can be used to interpret the significance of potential changes recorded from an electrode in the neighborhood of the end of a fiber tract immersed in a conducting medium. In order to investigate this case and to verify the above theoretical predictions a model of the callosal system was set up which consisted of a frog nerve suspended in a beaker of Ringer's fluid with both ends just reaching the surface a few centimeters apart. One end of the nerve was stimulated and records were taken by means of a micropipet inserted in the nerve at various points along its axis. When the electrode was in the nerve some distance from the end a triphasic wave was recorded in which the negative component was by far the most prominent. This is in agreement with the theoretical predictions. When the electrode was on the surface at the end of the nerve, a pure positive wave was obtained. Further, when this end of the nerve was lowered in the solution and the electrode placed at its end, a pure positive wave was again recorded. This shows that if a nerve impulse is traveling toward an electrode, but does not quite reach it, a positive wave will be recorded. It will be seen that the records of Fig. 2 fit this nerve model picture almost perfectly. Here on raising the electrode the negative wave of the callosal fibers does not change until a depth of about 0.5 mm. is reached, where a positive component starts to enter, indicating that some fibers have ended before they get to this point, but the fact that it does not completely reverse until the upper part of the first layer is reached shows that a considerable fraction of the fibers extend this far.

Turning to the origin of the negative part of the cortical wave as amplified by strychnine, Fig. 4 shows records taken with a monopolar micropipet at different depths in a strychninized area. Here it will be seen that reversal takes place at a depth of about 0.8 mm. and that the wave remains

positive as far as it can be followed in the white matter. The depth at which the reversal occurs seems to be quite variable.

The theoretical interpretation of the records taken with strychnine is not completely clear, but several points seem quite definite. The wave is always negative to a surface electrode and positive to an electrode in the deeper cortical layers and adjacent white matter, and the transition from one to the other is not a smooth process. If the electrode is placed at the point of minimal potential and the amplification increased, a number of small asynchronous waves can be seen, some positive and some negative. This indicates that a large number of cortical elements contribute to the production of the potential as measured at the surface, and these elements may be some distance apart in the cortex. It is possible to explain this potential on the basis of summated axon action potentials, just as in the case of the initial positive potential. It seems to indicate impulses which are initiated in the first cortical layer and travel to the deeper layers, as far as layer V. The positive potential in the deeper layers would then be due, as before, to impulses traveling toward the electrode but stopping before they reach it.

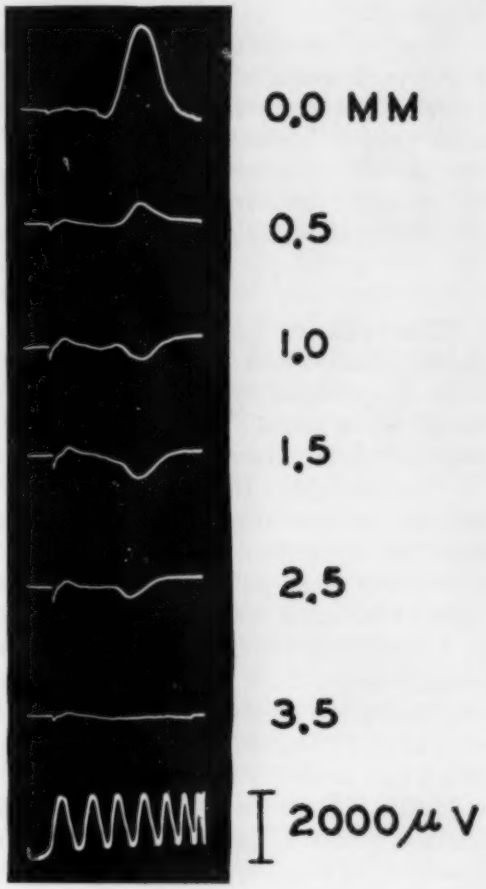

FIG. 4. Potentials recorded with a unipolar micro-electrode at various depths below the surface of the middle suprasylvian gyrus in response to contralateral cortical stimulation. All records were taken after the local application of 1.0 per cent strychnine sulfate at the site of entry of the recording electrode. An upward deflection indicates that the active electrode was negative with respect to the indifferent electrode. Time record, 60 cycles.

On applying strychnine to the cortex while recording from a surface electrode, there is, in addition to the enormous enhancement of the negative wave, some enhancement of the initial positive wave. If, after an area has been strychninized for some time, a small amount of cocaine is added, the negative wave disappears within a few seconds, leaving the enhanced positive wave. As the cocaine penetrates deeper into the cortex the enhancement of the positive wave gradually

disappears. After about 3 min. the initial positive wave reaches normal size. It is difficult to follow the enhancement of this wave within the cortex, but it is believed that it reverses in sign at a level about 0.1 mm. below the surface and is measurable to a depth of about 0.6 mm. Thus this enhancement can be explained as being due to the discharge of an additional group of fibers originating in layers II and III of the cortex and terminating in layer I.

Each of the convulsant drugs which was used has its own peculiarities. While no systematic attempt has been made to differentiate between them, a few of the more striking dissimilarities may be noted. *Picrotoxin* is the most potent, is slow to act, and its effect lasts for several hours. *Metrazol* acts rapidly, but exerts its effect for only a few minutes. *Strychnine, acetylsalicylic acid* (aspirin) and *camphor monobromide*, listed in order of potency, act in 5–15 minutes and produce effects for 30–40 minutes.

Discussion

The evidence presented seems to point strongly to the view that convulsant drugs lower the threshold for synaptic transmission, and that narcotic drugs block synaptic transmission before they block conduction in axons. These ideas, of course, are by no means new, and the drugs were used here only to facilitate the interpretation of the normal records.

The conclusion that the afferent fibers of the callosum ramify in the second and third cortical layers and end in the first layer is in good agreement with the anatomical findings of Kölliker (1896) and Lorente de Nó (1922, 1938), but is in disagreement with those of Kappers, Huber and Crosby (1936) who state that the fibers of the corpus callosum end in layer III.

Undoubtedly cortical stimulation sets up antidromic conduction in many callosal fibers. This phenomenon can hardly affect the conclusions drawn concerning the origin of the second or postsynaptic part of the wave. The cell bodies of callosal fibers lie in layers III, V and VI (Pines and Maimam, 1939), and probably have dendrites and recurrent collaterals reaching as far as layer II (Lorente de Nó, 1938). It is therefore possible that the initial (surface positive) potential may be due in part to antidromic impulses. However, in studies on the monkey (Curtis, 1940b) stimulation of a point, *A*, on one side, sometimes produced two large potentials on the contralateral hemisphere, one at the symmetrical point, *B*, and another at a point, *C*, some distance from *B*. When the stimulating electrodes were placed at *C* and the recording electrode at *A*, no potential change was recorded. For this reason it has been concluded that antidromic conduction plays at most only a minor rôle in the production of the potential as recorded at the surface. The conclusion that callosal afferents extend to layer I is thus not invalidated by the possibility that cortical stimulation may set up antidromic impulses in callosal fibers. On the other hand, the conclusion that callosal afferents ramify in layers II and III is not conclusively proven by the present work.

The relatively long delay which sometimes occurs between the arrival of the afferent impulse and the initiation of the evoked strychnine spike is interesting. When a convulsant drug is placed on the cortex, the first effect is a gradual increase in the size of the negative wave as recorded from the surface. When this wave reaches a size several times its initial value an enhancement of the positive wave can usually be detected, and since the latency to crest is also increased the change must be due to impulses arriving somewhat later than those which cause the original positive wave. After some time (10 to 15 min. for strychnine) two positive waves, about 20 msec. apart, are seen in the records; sometimes the interval is as great as 100 msec. The first of these is the original positive wave; the second is the initial portion of the strychnine spike. When these two waves are separated it can be shown, by varying the strength of the stimulus, that the strychnine response is all-or-none; such, however, is not the case in the early stages. Investigation of the initial positive part of the strychnine response by means of microelectrodes suggests that this potential is due to a discharge of impulses to the surface from about the level of the third layer. On this basis a typical strychnine spike will be produced only after sufficient time has elapsed to allow strychnine to penetrate to this level. The results obtained with strychnine in this work are in agreement with those of Dusser de Barenne and McCulloch (1938). When picrotoxin was placed on a point in the motor cortex, a typical "strychnine" response to contralateral cortical stimulation was produced in about 20 min., but 40 to 60 min. elapsed before a muscle twitch ipsilateral to the stimulated side was observed as a result of this response, and no difference was recorded in the potential wave when the twitch occurred. That the muscle response observed was due to activation of the contralateral motor area was demonstrated by its disappearance after local applications of nembutal to this area. Presumably it took 40 to 60 min. for the picrotoxin to penetrate to the deeper cortical layers where it facilitated conduction across synapses involving cortical efferent neurons.

Taken together the results presented in this paper indicate that the typical response to the application of a convulsant drug to the cortex originates in the third layer, is conducted to the first layer by interneurons where synaptic connection is made with other interneurons which conduct it to the deeper cortical layers where in turn synaptic connection may be made with cortical efferents.

Summary

In cats under barbiturate anesthesia single electrical shocks applied to the cortex of one cerebral hemisphere evoke potentials at one or more points on the cortex of the other hemisphere. These responses are mediated by the corpus callosum. The potential wave is typically diphasic; it is composed of an initial surface positive component lasting about 15 msec. and a surface negative component lasting about 75 msec. If a convulsant drug such as picrotoxin is applied to the surface of the pia under the pick-up electrode the

negative component is greatly increased in magnitude and the positive component is increased slightly. If an anesthetic drug such as nembutal is applied, the negative component is completely obliterated but the positive component undergoes no change.

By inserting micro-electrodes to various depths in the cortex and underlying white matter during the action of convulsant and narcotic drugs it has been possible to gain some knowledge of the origin and course of the impulses which give rise to the potential changes recorded from the pial surface. The results indicate that the ascending fibers of the callosum ramify in the upper layers of the cortex and end in the first layer where they make synaptic connections with descending interneurons which lead to the deeper cortical layers. The ascending fibers give rise to the surface positive component of the wave, the descending internuncial fibers to the surface negative component.

The author wishes to express his appreciation to Dr. Philip Bard for his advice in all parts of this work.

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FUNCTION OF MESENCEPHALIC ROOT OF FIFTH CRANIAL NERVE*

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THE MORPHOLOGY of the cells giving rise to the mesencephalic root of the Vth cranial nerve has been carefully studied by many observers. The resemblance of these cells to the unipolar primary sensory cells of the cerebrospinal ganglia was noted by Allen (1919), Clark (1926), Weinberg (1928), Schneider (1928) and Sheinin (1930). Clark (1926) demonstrated the close similarity of the large cells of the mesencephalic nucleus and those of the spinal ganglia which Warrington and Griffith (1904) demonstrated to be connected with muscle spindles. Because of this resemblance, and because of the peripheral distribution of the majority of the mesencephalic root fibers to the masticator branches of V, the consensus of opinion of workers on this subject has been that the mesencephalic root represented primary sensory fibers mediating muscle sensibility from the muscles of mastication (Johnston, 1909; May and Horsley, 1910; Willems, 1911; Kosaka, 1912; Allen, 1919; and Thelander, 1924). Furthermore, it was recently demonstrated that mesencephalic root fibers, in addition to passing peripherally with the masticator branches of V, pass into those purely sensory branches (superior alveolar, inferior alveolar and palatine nerves) which supply deep sensation to the teeth, gums and hard palate (Corbin, 1940). Central collaterals from the mesencephalic root were seen passing to the motor nucleus of V by Cajal (1896), Wallenberg (1904), May and Horsley (1910) and others.

Pfaffmann (1939) obtained action potentials from the superior alveolar nerves after touch or pressure applied to the teeth, gums and adjacent lips. The impulses were slow to adapt and conducted quite rapidly, which would indicate that they were mediated by fairly large myelinated fibers. Removal of the dental pulp and destruction of the nerves in the apical canal by cautery did not affect these reponses. Pfaffmann concluded that the majority of the endings giving rise to these impulses are located in the periodontal membrane. Lewinsky and Stewart (1937) found that the larger myelinated fibers formed peculiar spindle-like endings in the periodontal membrane, and concluded, as a result of the work of Stewart (1927), that these spindles reacted primarily to pressure stimuli.

Pfaffmann also obtained strong and sudden movements of the mandible on sectioning the maxillary nerve. In addition to this observation, Sherrington (1917) found that blunt pressure stimulation of the gums bordering the teeth of both the upper and lower jaws, of the tooth crown, as well as of the hard palate, caused reflex opening of the tonically closed jaw in the decerebrate cat, involving reflex inhibition of the jaw-closing muscles as well as stimulation of the opener muscles. The evidence presented by these two workers, in addition to his own histological findings, led Corbin (1940) to postulate mediation of the afferent limb of this reflex arc by the mesencephalic root fibers which he found in the sensory branches of V. Certain workers have assigned other functions to the mesencephalic root cells. Freeman (1925), Sheinin (1933) and Woollard (1931) suggest, on the basis of studies on chromatolytic mesencephalic nucleus cells, that this nucleus is the source of the sensory fibers to the extrinsic ocular muscles, in contradistinction to the evidence presented by Kohnstamm and Quensel (1908) and Tozer (1912).

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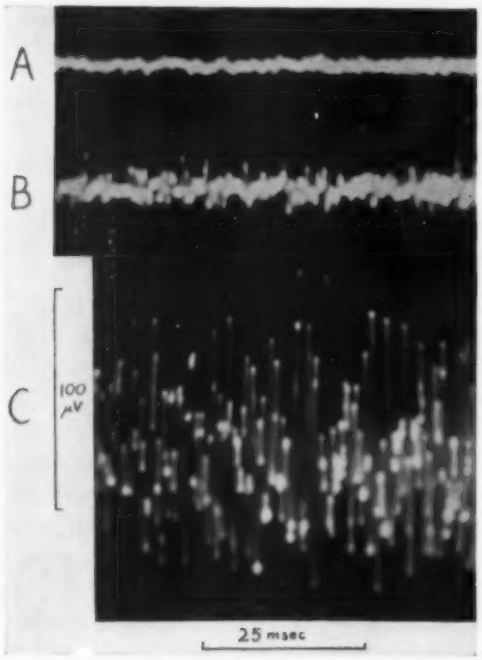

FIG. 1. Photographs of single sweeps of oscillograph. Velocity and amplification unchanged. Cat 83. A. Noise level of amplifier. B. Background activity of mesencephalic nucleus. Jaw closed. C. Activity recorded from the same point as record B when jaw was depressed. This represents a response recorded as 5+.

On the basis of stimulation and chromatolytic experiments, Lewy, Groff and Grant (1937, 1938) suggest that this nucleus gives rise to autonomic fibers passing peripherally with the three trigeminal divisions, and that stimulation of these autonomic fibers results in the pseudomotor response in degenerating facial and tongue muscle. Critical analysis of the findings of these workers will be reserved for the discussion.

There is no definite physiological evidence concerning the function of the mesencephalic root of the Vth cranial nerve. Considerable evidence gathered on the anatomical side suggests its logical rôle in the control of mastication. It has been the purpose of the experiments here reported to obtain irrefutable evidence regarding its function.

For this purpose the Horsley-Clarke stereotaxic instrument has been employed to place a unipolar lead within the mesencephalic root. Action potentials were led to a cathode ray oscillograph and loud speaker. The ease with which action potentials could be elicited from the mesencephalic root in response to jaw opening has been gratifying as have the selectivity and sensitivity of the response.

MATERIAL AND METHODS

Twenty adult cats were used in these experiments. Under light nembutal narcosis (30 mg./kg.) the Horsley-Clarke instrument was placed on the animal's head. The machine was suspended from a support in order that the jaw might be easily manipulated. A single 22 gauge nichrome wire, insulated with several coats of baked enamel except for a 0.5 to 1.0 mm. sharpened tip, was used as a unipolar lead, the machine itself being the other lead. (Potentials have also been recorded with a concentric electrode.) Action potentials were led through a 5 stage resistance coupled amplifier with a differential input (circuit of Toennies, 1938) to a cathode ray oscillograph and loud speaker. The entire brain stem in the region of the mesencephalic root and nucleus, from a level well rostral to the oculomotor nucleus to levels well caudal to the exit of the Vth nerve, was explored. The needle carrier of the Horsley-Clarke machine was tilted rostrally 35° so that the needle might pass to points caudal and ventral to the bony tentorium cerebelli without striking it (Fig. 2). This procedure avoided the necessity of removing the tentorium or entering caudal to it. The use of the Horsley-Clarke rotating needle carrier was described by Harrison (1938).

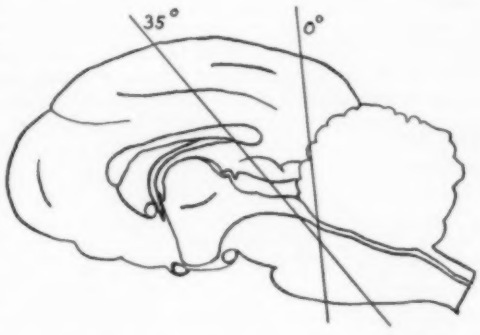

FIG. 2. Sketch of sagittal section of cat's brain. The line marked 0° indicates normal vertical plane of Horsley-Clarke machine. Line marked 35° indicates plane used in these experiments.

The technique consisted of inserting the needle into the brain along a line calculated to pass through the mesencephalic root. Stopping well above the predetermined root level, potentials were recorded before, during and after opening the jaw. A lucite or glass rod was used to depress the jaw. The needle was then projected 0.5 mm. deeper, the jaw response recorded, and so on. In this manner the entire root was explored and its position mapped out. If no potentials were elicited through jaw opening, a new insertion of the lead was made 1 mm. lateral or medial to the first one. We were usually successful in striking the root on the first puncture.

In 6 cats, the mandibular nerve was exposed extracranially just distal to its exit through the foramen ovale prior to the placing of the Horsley-Clarke machine on the cat's head. An electrode was then inserted into a rostral portion of the mesencephalic root, the insertion being halted when the first detectable impulses were elicited by jaw opening. The mandibular nerve was then transected and another attempt made to elicit responses from jaw opening. The entire rostro-caudal extent of the root was then explored, using the previously determined lateral coordinates, and testing for responses from passive movement of the eyes, from tactile stimulation of the skin of the head and the buccal mucosa, and especially from blunt pressure on the teeth and palate.

Using silver-silver chloride electrodes, responses have also been recorded from the inferior alveolar, superior alveolar, palatine, infraorbital, and ethmoidal nerves during blunt pressure stimulation of the teeth and gums, as well as tactile stimulation of the skin of the head, nasal and buccal mucosa.

Critical points, such as those from which exceptionally high potentials were obtained, were marked by placing a small electrolytic lesion at a point 1.5 mm. lateral to the path of the unipolar electrode (Fig. 3, 4, 5 and 6).

In all experiments, following completion of the above procedures, the head of the animal was injected with 10 per cent formalin and the brain removed to formalin. On the following day, the brain stem was sectioned as nearly as possible in a plane parallel to the path of the unipolar electrodes, *i.e.*, in a plane which lay at a 35° angle to the vertical plane of the Horsley-Clarke machine (Fig. 2). This angle of cutting accounts for the obliquity of the sections included in the illustrations. The brains were subsequently embedded in nitro-cellulose, sectioned at 40μ, every other section mounted and stained according to the Weil technique. All experimental results were then carefully checked in the microscopical preparations.

Observations

Action potentials recorded from within the central nervous system vary according to the neural structure with which the electrode is in contact, and with the physiological condition of the animal (Gerard *et al.*, 1936). As the electrode moves through the brain, injury potentials are elicited; these quickly disappear, leaving only the amplifier background plus the background of the particular region. The action potentials which have been elicited from the mesencephalic root of V by opening the jaw have been larger than any which have been specifically evoked from other portions of the brain stem incidentally studied in connection with this problem. When the electrode tip is actually within the mesencephalic root and the jaw is opened, the markedly heightened and more numerous action potentials are easily seen on the oscillographic screen (Fig. 1), and a roar is heard from the speaker. This response is prolonged throughout the period of jaw opening. Extension of the masticator muscles by gravity alone was sufficient to evoke an excellent response, while further extension gave rise to potentials as much as six times the height of the background activity (Fig. 1). The response to jaw extension was entirely abolished by passive closure of the jaw.

The best responses were obtained when the electrode was at its first position within the root and had not been withdrawn and reinserted. After

withdrawal, or projection and partial withdrawal to the original point, action potentials could still be elicited from jaw opening but were usually diminished in number and amplitude due to damage to the root.

The specificity of the response may be indicated by stating that on all occasions when the electrode passed approximately 0.5 mm. to either side of the root there was little response to jaw opening. Only a faint muffled roar was heard when the needle tip was this distance from the root. Such a response characterized proximity of the needle to the root, but was quite different from the response elicited from direct contact with it.

The response to jaw opening was maintained as long as the jaw was depressed and in that respect is in complete conformity with proprioceptive action potentials obtained elsewhere. Similar responses could be elicited by pressing on the homolateral masticator muscles or by pressing back the eyeball and thus indirectly pressing on the pterygoids (*sic*), a characteristic of the proprioceptors within striated muscle.

Because of the sensitivity and amplitude of the masticator stretch response, it is essential to eliminate this response before further study of mesencephalic root function. Both before and after section of the mandibular root, movement of the eyeball in any direction, and therefore stretch of the extrinsic ocular muscles, failed to produce potentials in any portion of the mesencephalic root. On the other hand, blunt pressure stimulation of the teeth of the homolateral half of the upper jaw, and especially of the homolateral canine tooth, resulted in a marked increase in the height and frequency of the action potentials obtained from the caudal half of the mesencephalic root (Fig. 6), in all 6 experiments in which the mandibular nerve was cut. This response may also be elicited from the teeth with the mandibular nerve intact, but the possibility of a response from jaw movement during stimulation is eliminated by section of the nerve. A response was also obtained from the homolateral hard palate, the most anterior portion adjacent to the canine teeth being the most sensitive region.

The canines were the most sensitive structures concerned in elicitation of potentials in the mesencephalic root following blunt pressure stimuli of oral regions. Pressure on these teeth in any direction resulted in a large burst of potentials from the caudal portions of the mesencephalic root (Fig. 6), lasting throughout the duration of the stimulus. Pressure on the gum or alveolar process overlying the canine tooth resulted in similar potentials. Pressure on the gums overlying the other homolateral teeth, sufficient to press on the underlying tooth roots, especially the incisors, evoked a response but to a lesser degree.

Except for the response resulting from jaw opening and the responses from blunt pressure stimulation of the teeth and hard palate, there were no responses from the mesencephalic root as the result of stimulation of other types from the head or buccal regions.

The mesencephalic root potentials are obtained solely from the homolateral masticator muscles, teeth and hard palate, never from contralateral

structures. Section of the mandibular division of V abolishes the jaw opening response in the mesencepahlic root on the same side, leaving the response intact on the opposite side. Exploration of the mesencephalon at A4.0 (anterior Horsley-Clarke coordinate) failed to yield potentials from jaw movement. Histological examination of the brain stems at this level showed that the needle punctures were immediately rostral to the rostralmost portion of the mesencephalic root of V.

In all experiments, punctures made through the mesencephalic root from its rostral level (approximately A3.0) to the level at which the root turns

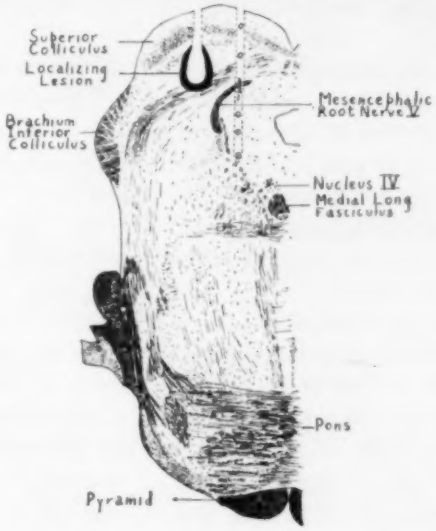

FIG. 3. Projection drawing of section of brain stem of cat 4 in plane of angle 35°, Fig. 2, at level of trochlear nucleus. The path of recording lead is indicated in dotted lines medial to localizing lesion. Numbers along path indicate intensity of response to depression of jaw. 3 indicates response of about 30 μV. See text for additional description.

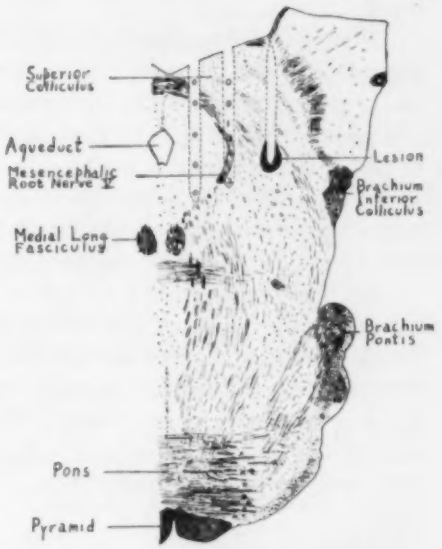

FIG. 4. Projection drawing of section of brain stem of cat 55, at level 1 mm. caudal to Fig. 3. 5 indicates a response of greater than 50 μV. Note complete absence of response to jaw opening from puncture medial to mesencephalic root.

laterally to enter the Vth nerve (approximately P7.0) gave rise to the characteristic response from opening of the jaw. The frequency of the action potentials was less from the rostral half of the root than from the caudal half, although the amplitude of the individual spikes was as great in one part as another. This decreased frequency of potentials in the rostral half is undoubtedly due to the diminished number of fibers in the root as it ascends in the mesencephalon.

When the electrode is inserted at or caudal to P8.0, a level histologically seen to be caudal to the laterally passing fibers of the mesencephalic root, no action potentials are obtained from opening of the jaw, or from pressure on the teeth or palate.

The selectivity and sensitivity of the responses from the mesencephalic root are well illustrated in the accompanying figures. All figures are actual line copies of projections of the brain stem (approximately 5×), the plane of section, as previously stated, being parallel to a plane at a 35° angle to the Horsley-Clarke vertical plane. The numbers within the electrode path indicate the absence (0) or presence (1 to 5, minimum to maximum response approximating 10 μV to over 50 μV) of action potentials to opening of the jaw. In Fig. 6 the numbers within the electrode path indicate the response to blunt pressure stimulation of the teeth and palate. The lesion in each figure is lateral to the electrode point yielding the maximum response at that level.

Figure 3 represents a section at A1.0, or through that portion of the mesencephalic root lying at the level of the trochlear nucleus in cat 4. The electrode path traverses the dorso-medial portion of the mesencephalic root at the point marked 3. The response elicited at this point by jaw opening was of the intensity which we have arbitrarily designated as 3+ (about 30 μV). It may be seen that the tip of the localizing lesion lies lateral to the maximum response. As the electrode passed ventrally, the response decreased and disappeared as the exposed tip left the root.

Figure 4 represents a section of the brain stem of cat 55 at A0.0, or 1 mm. caudal to the plane of Fig. 3. Here the electrode passed through most of the fibers comprising the mesencephalic root at this level. The number 5 (more than 50 μV) indicates a maximum response at a point where the electrode tip was in direct contact with the main body of the root and lies directly medial to the localizing lesion. Note the complete absence of all response to jaw opening in the medial electrode path which misses the mesencephalic root.

Figure 5 represents a section just rostral to the decussation of the trochlear nerve. Here, as the electrode tip lay immediately lateral to the dorsal portion of the mesencephalic root, 1+ to 2+ (10 to 20 μV) responses were obtained. Then, as the tip came to lie directly in the root medial to the localizing lesion, there were responses of maximal intensity (4+ to 5+). The response disappeared as the electrode passed ventral to the root.

Figure 6 represents a section through the opposite half of the brain stem of the same animal and at the same level as Fig. 5. On this side the mandibular nerve was sectioned before inserting the electrode at this level. While the electrode tip was medial to the lesion and within the mesencephalic root, action potentials were elicited from blunt pressure stimulation of the homolateral upper teeth and palate. A 3+ response was as large as was ever obtained from the teeth and then only by pressure on the homolateral canine tooth, the other homolateral teeth and palate giving a response of lesser magnitude. There was no response to jaw opening on this side after section of the mandibular nerve. Careful study of this illustration (and of the microscopical sections) shows that the needle was rostral to the level of the main sensory

nucleus of V, and almost 3 mm. medial to the position of this nucleus. Tactile stimulation of the palate, gums and other oral structures failed to elicit this response, although leads within the main sensory nucleus of V or the sensory root yield responses to such stimuli.

Leading from the inferior alveolar nerve, action potentials similar to those described for blunt pressure stimulation of the upper teeth are easily elicited by similar stimulation of the homolateral lower teeth, especially the canine. Tactile responses from the skin of the anterior portion of the lower jaw were also elicited from the inferior alveolar nerve, whereas tactile responses were never obtained from the mesencephalic root. It is difficult to press on the teeth of the lower jaw without depressing the jaw and thus stretching the masticator muscles. No attempt, therefore, was made to record the effect of blunt pressure stimulation on the lower teeth from the mesencephalic root.

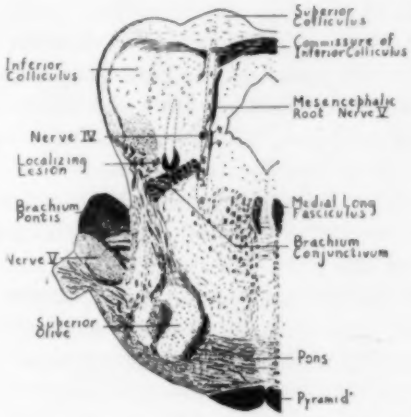

FIG. 5. Projection drawing of section of brain stem of cat 10 at level just rostral to trochlear decussation. Note that response to depression of jaw is 1 (10 μV) as needle lies immediately lateral to mesencephalic root and increases (3, 4 and 5; 30 to over 50 μV) as needle enters root.

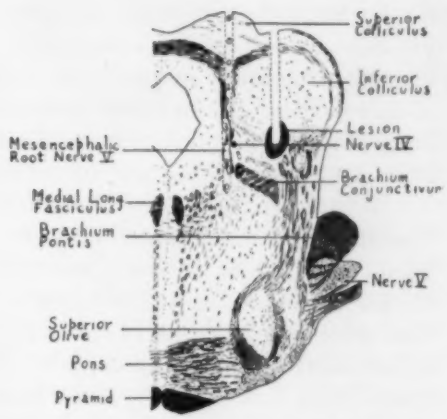

FIG. 6. Projection drawing of section of brain stem of cat 10, at same level but opposite side as Fig. 5. The mandibular nerve had been sectioned and responses noted were obtained from blunt pressure on upper teeth and hard palate. The response to depression of jaw was negative. A 3 represents maximum response obtained from stimulation of teeth and palate. Other data as in Fig. 3 and in text.

Leads from the superior alveolar and palatine nerves gave similar responses to blunt pressure stimulation of the upper teeth and palate, here again the canine being by far the most sensitive structure. Leads from the infraorbital nerves, central to the separation of the superior alveolars, gave in addition to the responses to blunt pressure stimulation of the teeth, tactile responses from the skin of the infraorbital region. We have been unable

to elicit potentials from the ethmoidal branch of the ophthalmic nerve on blunt pressure or tactile stimulation of the teeth, palate, snout skin or nasal mucosa.

Discussion and Conclusions

Action potentials have been elicited from the entire extent of the trigeminal mesencephalic root upon stretching the muscles of mastication. These responses have been identical with the proprioceptive impulses from peripheral nerve on stretching striated muscle (Mathews, 1933; Corbin and Harrison, 1938, 1939). They are slow to adapt, elicitable by pressure over the muscles concerned, and immediately abolished by section of the masticator nerves. Although the conduction rate of these impulses has not as yet been determined, the size of the potentials recorded indicates that we are dealing with fairly large fibers. Occasionally, on entering the mesencephalic root, we have elicited well spaced, regular potentials such as are obtained from single fiber preparations. Such individual potentials have always been large and undoubtedly mediated by single, large myelinated fibers.

Responses have been evoked when leading from the caudal half of the mesencephalic root from blunt pressure stimulation of the upper teeth and hard palate. Only lesions of the caudal half of the mesencephalic root and nucleus resulted in appreciable degeneration in the palatine and alveolar nerves, thus explaining our inability to obtain tooth and palate responses from the rostral half of the mesencephalic root (Corbin, 1940). These responses and those from jaw opening have been recorded from the mesencephalic root alone, not from immediately surrounding nervous tissues. Tactile stimulation of the skin of the head or buccal mucosa did not evoke responses from this root.

The area of distribution for the peripheral receptors for these responses corresponds precisely with the distribution of the mesencephalic root fibers as determined in degeneration experiments (*vide supra*). As previously mentioned, the histological studies demonstrated mesencephalic root fibers in the superior alveolar and palatine branches of the maxillary division of V as well as in the masticator and inferior alveolar branches of the mandibular division. Mesencephalic root fibers were also found in the ethmoidal branch of the ophthalmic nerve, but we have been unable in the work here reported to find any function for these fibers.

Action potentials have been obtained from the mesencephalic root fibers on jaw opening after these fibers have turned laterally and left the region of their nucleus, action potentials which were identical with those obtained from the ascending portion of the root. Primarily because of the evidence from degeneration experiments on this root (*vide supra*), it may be assumed that we have been recording from primary sensory neurons. The close similarity of the mesencephalic root potentials to the proprioceptive potentials which have been studied in the spinal accessory nerve substantiates this belief. However, one would have to determine accurately the conduction time to rule our the possibility of a post-synaptic component.

The responses here reported have been from the homolateral teeth, palate and masticator muscles, never from contralateral structures. This again is in complete agreement with our anatomical studies on the root, although Lewy, Groff and Grant (1938) suggest, on the basis of chromatolytic studies, that a goodly portion of the mesencephalic root V fibers cross to the opposite side. Corbin (1940) has discussed the evidence indicating that the receptors for deep pressure from the teeth are located in the periodontal membrane. Muscle spindles have been seen in the external pterygoid and masseter muscles of the rabbit (Cipollone, 1897) and in the masseter muscle of the fetal pig (Cuajunco, 1926). It is likely that similar endings in the masticator muscles of the cat give rise to the impulses which we have recorded in the mesencephalic root during stretch of these muscles.

The medullated fibers which arise from the medium to large sized cells of the mesencephalic nucleus of V may then be considered as forming the afferent limbs of masticator reflex arcs. The findings by Pfaffmann (1939) and Sherrington (1917) that mechanical stimulation of the maxillary nerve causes reflex jaw opening, and Sherrington's observations on decerebrate cats in which he demonstrated jaw opening from blunt pressure stimulation of the teeth, gums and palate, indicate that those mesencephalic root fibers arising from the periodontal membrane (especially of the canines in the cat) and palate mediate impulses which are inhibitory to the trigeminal motor nucleus cells. Acting in conjunction with these impulses are those arising from the muscles of mastication, the total mesencephalic root inflow thereby controlling and coordinating movements of the lower jaw, permitting a forceful bite without damage to the structures involved in mastication (*i.e.*, teeth, gums, and palate).

Bremer (1923) sectioned the mesencephalic root of V just rostral to the trigeminal motor nucleus in decerebrate cats and observed no decrease in tonicity of the masticator muscles in the majority of his animals. Because of this finding he concluded that the mesencephalic nucleus and root were not concerned in reflex activity of the masticator muscles. He admits that this evidence was from acute experiments lasting only a few hours, and that therefore such a section would not interrupt the afferent limb of the mesencephalic root to the motor nucleus of V, but would merely sever such fibers from their cells of origin. This leaves intact the mesencephalic root collaterals from the pseudo-unipolar cells of its nucleus to the motor nucleus of V. That such collaterals, severed from their cells of origin but retaining their peripheral connections, might maintain their functional activity for even a day or two is supported by the findings of Gibson (1940) who demonstrated maintenance of function in degenerating preganglionic cervical sympathetic fibers for two days following nerve section.

Rioch and Lambert (1934) found in 4 acute experiments and in one chronic experiment that section of the sensory root of V abolished the jaw-jerk and that there was complete flaccidity of the jaw closing muscles on the side of the lesion. These results are difficult to explain except on the basis of

possible damage to mesencephalic root fibers as they enter the brain stem.

We definitely feel, as a result of the morphological evidence reviewed and the physiological evidence of these experiments, that regardless of what other function or functions the mesencephalic root may be found to have, its fibers do mediate primary proprioceptive impulses from the muscles of mastication and deep pressure impulses from the teeth and hard palate.

The absence of responses in the mesencephalic root of V to types of stimulation of the head region other than the blunt pressure and stretch stimuli described offers another example of the central segregation of sensory functions, whereas the peripheral trigeminal branches contain sensory components of many types.

No action potentials could be evoked from any portion of the mesencephalic root of V as the result of passive movement of the eyeball; nor could any potentials of a sensory nature be obtained from leads placed directly on the oculomotor, trochlear and abducens nerves during extension of the extrinsic ocular muscles (unpublished data). This does not mean, however, that muscle sense fibers from the extrinsic ocular muscles may not have their cells of origin in the mesencephalic nucleus of V. It may well be that the sensory endings present in the extrinsic ocular muscles (Cilimbaris, 1910; Hines, 1931) do not respond to stretch, such as does the usual type of muscle spindle, but only to contraction of the muscles they innervate. We are at present attacking the problem with this possibility in mind. We can state now, however, that stretch of the extrinsic ocular muscles does not set up potentials which are of the usual proprioceptive type.

The results here reported lend no support to the findings of Lewy, Groff and Grant (1938), who believe that the mesencephalic root contains cells giving rise to cranial autonomic fibers which course peripherally with the branches of V and the stimulation of which leads to the pseudomotor phenomenon in the properly denervated striated musculature. Using the technique described in our experiments for accurately locating a stimulating electrode within the mesencephalic root no pseudomotor (Vulpian-Heidenhain) phenomenon could be elicited in chronically denervated tongue preparations, although this was easily obtained from stimulation of the reticular matter in the region of the VIIth nerve well caudal to the lowermost fibers of the mesencephalic root (Corbin, Harrison and Wiggington, work in progress). It may be assumed that the intense stimuli which Lewy, Groff and Grant believed they were applying to the mesencephalic root, actually spread to autonomic neurons located at lower levels.

The numerous theories regarding the function of the mesencephalic root and nucleus of V, advanced by early workers in neuroanatomy, may be dismissed for the most part without serious consideration. Castaldi (1926), on purely morphological grounds, has revived the theory that this root is motor in function. However, the majority of contemporary workers who have studied this nucleus histologically have concluded that the cells comprising it

closely resemble the sensory cells of the cerebrospinal ganglia (Allen, 1919; Clark, 1926; Weinberg, 1928; and Sheinin, 1930). It would seem that the physiological evidence presented in this paper must certainly rule out the possibility of a motor function for the majority of the cells in this nucleus. Furthermore, an admixture of sensory and motor neurons in the same nucleus, wholly contrary to the findings elsewhere in the central nervous system, would make it extremely unlikely that any motor cells, either autonomic or somatic, are located in the mesencephalic nucleus of the Vth cranial nerve.

Summary

1. Using the Horsley-Clarke stereotaxic instrument for localization, action potentials in 20 cats have been picked up from the mesencephalic root of the Vth cranial nerve with a unipolar lead to a 5-stage resistance-coupled amplifier with a differential input and then to a cathode ray oscillograph and loud speaker.

2. Action potentials, characteristic of proprioceptive impulses elsewhere, have been elicited from all portions of the mesencephalic root in response to opening of the jaw and thence stretch of the masticator muscles. Careful histological study of the brain stems has demonstrated that this response was elicited only when the lead was within the homolateral mesencephalic root, never from surrounding neural structures or the contralateral root.

3. From the caudal half of the mesencephalic root action potentials have been elicited also from blunt pressure stimulation of the homolateral teeth and hard palate. In the cat, the canine teeth have been by far the most responsive of the oral structures.

4. The physiological evidence here presented demonstrates the function of those mesencephalic root fibers found in degeneration experiments to enter the alveolar and palatine nerves. Impulses traversing these fibers to the motor nucleus are probably chiefly inhibitory, preventing damage to the structures concerned in biting (gums, teeth and hard palate). These impulses and those passing over the masticator nerves from the muscles of mastication, mediated by the mesencephalic root fibers, constitute the afferent limbs of masticator reflex arcs, thereby coordinating and controlling chewing movements.

5. No action potentials have been elicited from the mesencephalic root of V or from the IIId, IVth or VIth nerves as the result of stretch of the extrinsic ocular muscles. The authors realize that this evidence does not exclude the mesencephalic root from a role in the sensory innervation of the ocular muscles.

6. Absolutely no evidence has been obtained to support the assertion by other workers that the mesencephalic nucleus gives rise to cranial autonomic fibers passing to facial and tongue muscles. On the contrary, evidence is presented which indicates that an autonomic function for mesencephalic root fibers is highly improbable.

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OCULOMOTOR NERVE AND REFLEX DILATATION OF PUPIL

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IN 1883 Bechterew concluded that the dilatation of the pupil resulting from painful stimulation is caused solely by inhibition of the activity of the third nerve. Although since that time Anderson (1904), Gullberg, Olmsted and Wagman (1938), and others have maintained that the sympathetic also participates in reflex dilatation of the pupil they have not denied that inhibition of the oculomotor nerve plays the chief part. In 1939 Ury and Gellhorn, after section of the third nerve in the cat, found that "under normal conditions the pupillary dilatation in response to pain is almost exclusively due to parasympathetic inhibition," while still more recently Ury and Oldberg (1940) concluded that the variability of the pupil to light or afferent stimuli is due wholly to variation in oculomotor tune.

FIG. 1. Cat no 2 four days after intradural section of the right oculomotor nerve. The pupil remained at this diameter (13 mm.) until the animal's death 4 months and 10 days after operation.

For some months we have had under study 20 cats in which the oculomotor nerve was sectioned intracranially. Observations made after the local application of eserine tend to support the conclusion of Ury and Oldberg. The failure of many recent physiological texts to assign to the oculomotor nerve its proper place in reflex pupillary dilatation warrants publication of observations which, though in part not original, confirm the view that reflex dilatation of the pupil is primarily an inhibition of the third nerve.

In the experiments to be reported one oculomotor nerve was sectioned intradurally through a temporal approach. In those instances in which the distal end of the nerve did not retract beyond the dura a short segment was removed from the proximal stump so that the two cut ends would not be left in apposition. Immediately after section of the nerve the pupil of that

side became dilated (Fig. 1). The dilatation was progressive until a permanent transverse diameter of about 13 mm. was attained. This maximal dilatation was not reached until recovery from the anesthetic. In cases in which ether was used it was accomplished within the hour, while with nembutal anesthesia it was not seen until the animal was fully awake some hours later. This difference apparently arises from a depressant effect of nembutal or other barbiturates on sympathetic tonus.*

The diameter of the pupil after third-nerve section remained 13 mm. throughout the period of study, which was from 2 to 6 months, except in two animals in which a narrowing subsequent to operation was proved at autopsy to be accompanied by gross and microscopic regeneration of the nerve. No change in the position or movements of the nictitating membrane was noted after oculomotor section. Although in some animals an apparent enophthalmos followed the operation it is believed that the operative deformity of the skull and the post-operative ptosis rendered this observation unreliable.

In 8 of the 20 animals in which the oculomotor nerve had been sectioned the sympathetic pathway to the iris was interrupted at a later date, either by sectioning the cervical sympathetic trunk or by removing the superior cervical ganglion or the stellate ganglion. Regardless of the method employed the pupil became narrowed to a new permanent diameter which varied from animal to animal within the range 7–10 mm. In cases in which the superior cervical ganglion or the stellate ganglion was removed this change was maintained indefinitely. In cases in which the operation consisted of section of the sympathetic trunk, regeneration after 3 or 4 weeks resulted in progressive enlargement of the pupil to the original diameter of 13 mm.

When only the oculomotor nerve was sectioned the pupil remained maximally dilated even though the animal was at rest. Such a pupil is not suitable for investigation of possible changes in sympathetic activity until it has been artificially constricted by addition of a miotic such as eserine. In every animal of this group it was found that when eserine was applied locally to the eyes there resulted a progressive constriction of both pupils. Without exception, however, throughout the period of advancing constriction the pupil on the side of the third-nerve section remained 1–2 mm. larger than the pupil of the normal eye, and when full eserine effect was obtained the pupil of the side operated upon measured approximately 2.5 mm. in transverse diameter whereas on the normal side the pupil measured only 1.5 mm. Thus the miosis produced by eserine was less in the parasympathectomized eye. With partial third-nerve regeneration, however, the normal response to eserine returned. An opposite modification was noted after

* That the drug exerts such an affect is evidenced by additional observations. The fully dilated parasympathectomized pupil could be reduced in diameter by inducing nembutal anesthesia. Moreover, under nembutal anesthesia the pupils were constricted and the nictitating membranes were protruded in normal animals, and in unilaterally sympathectomized animals sympathetic activity was depressed to such an extent that no difference in the response of the two pupils to the withdrawal of light could be observed.

the sympathetic was interrupted. In this case the eserine response was increased and this was true both in animals in which the parasympathetic path was intact and in those in which it had been severed. Our experiments shed no light on the nature of the diminished response to eserine following preganglionic parasympathectomy. With regard to the augmented response

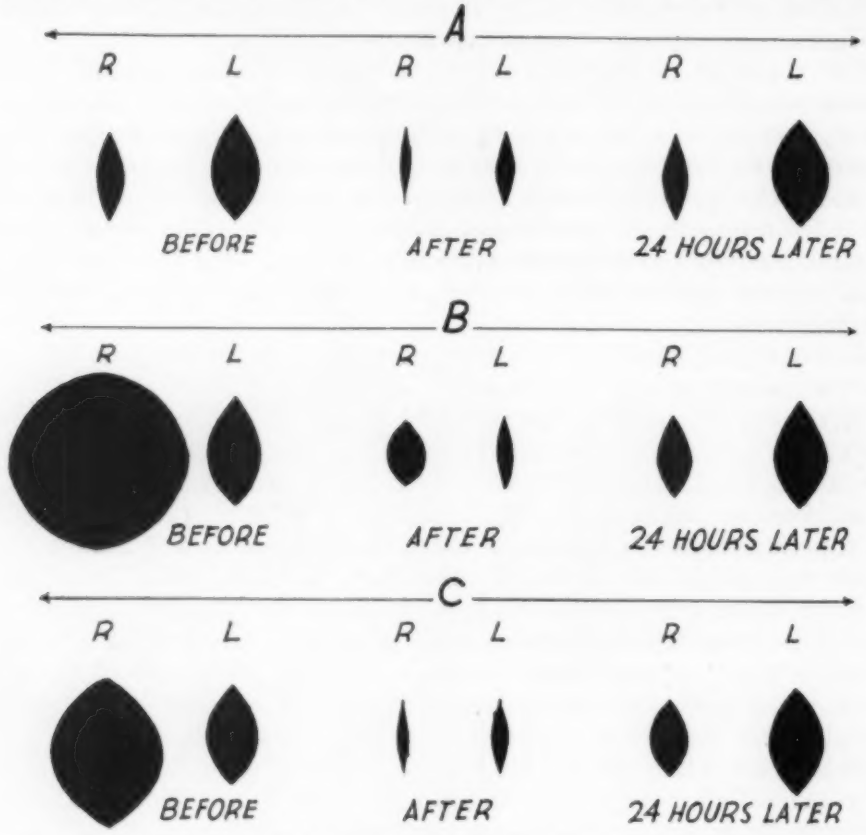

FIG. 2. Pupils before and after instillation of eserine into both eyes following (A) section of the right cervical sympathetic trunk, (B) section of right N. III, and (C) section of the right cervical sympathetic trunk and section of right N. III.

following sympathectomy it is reasonable to assume that it results from withdrawal of sympathetic dilator tone, which, when present, opposes eserine constriction.

Although the degree of constriction in response to eserine was decreased by parasympathectomy, the duration of the miotic effect was prolonged. Even after 24 hours, when the normal pupil had regained full activity, the parasympathectomized pupil still showed a decided constriction. This observation has been recorded previously (Anderson, 1905; Shen and Cannon, 1935). We have noted that subsequent sympathectomy did not alter this prolongation of the eserine effect.

These variations in response to eserine are shown diagrammatically in Fig. 2.

In a number of animals prepared by interruption of N. III and local application of eserine we attempted to evaluate the role of the sympathetic in pupillo-dilatation. Responses to the following stimuli were studied: (i) dark adaptation, *i.e.*, withdrawal of the normal light stimulus, (ii) painful stimulation such as electrical stimulation of the peri-anal skin or strong faradic stimulation applied directly to the sciatic nerve exposed under light ether anesthesia, and (iii) emotional excitement aroused by restraining the animal upon its back or exposing it to the barking of a dog. During the stages of partial eserinization the pupil of the normal eye dilated instantly in response to each of the stimuli listed, but there was never the slightest visible dilatation of the pupil on the side of the third-nerve section.* After the eserine effect was complete the dilator response of the normally innervated iris was usually reduced and in some instances abolished. The sympathetic dilator path was still intact since both pupils responded readily to faradization of the cervical sympathetic trunks.

From these experiments it is apparent that inhibition of the activity of the third nerve constitutes the principal factor in the reflex pupillo-dilatation elicited by (i) withdrawal of light, (ii) painful stimulation, and (iii) emotional excitement. This conclusion was confirmed in another series of experiments in which the effects of these forms of stimulation were determined in 6 animals in which only the sympathetic pathway was interrupted. Observations made immediately following operation and after the elapse of some days were as follows:

(i) The sympathectomized pupil dilates readily on withdrawal of light. Under nembutal anesthesia no difference between the two pupils was observed in this respect. In the unanesthetized state, however, it was noted that while the response was prompt on the side of the operation the dilatation was not as great. Gullberg, Olmsted and Wagman (1938), using infrared photography, noted that dilatation was prompt but slower in rate following sympathectomy and in some instances we have noted such retardation.

(ii) The sympathectomized pupil dilated readily in response to faradic stimulation of the sciatic nerve. The maximum diameter attained by the pupil on the side of the operation was never as great as that of the opposite pupil but the response was equally as prompt.

(iii) After sympathectomy the pupil underwent immediate dilatation in response to emotional excitement. Again, however, the dilatation was less than in the normal eye. An exception was noted in animals in which the superior cervical ganglion was removed. After an interval of 48 to 72 hours prolonged periods of emotional excitement led to augmentation of the dilatation. This augmentation, which appeared after some seconds, was much greater and more prolonged in the sympathectomized eye. It could be reproduced by the intravenous administration of 1 cc. of 1:100,000 adrenalin,

Therefore it was considered to be an adrenalin effect accompanied by sensitization on the side of the ganglionectomy. Thus, in addition to the immediate dilatation due to parasympathetic inhibition, prolonged emotional excitement gave rise to an adrenalin effect. The delayed adrenalin dilatation was distinguished easily from the prompt dilatation of third-nerve inhibition, for, in the latter case, periods of dilatation alternated rapidly with periods of constriction, the changes coinciding with momentary variations in the affective state.

Although Ury and Gellhorn (1939) concluded that pain stimuli elicit a dilatation of the pupil mainly by inhibiting the center of the third nerve, they stated, "What paths are involved in emotional excitement remains to be seen." That dilatation in response to emotional excitement is also effected through inhibition of the third nerve is evident, since this form of stimulation evokes immediate dilatation in the sympathectomized pupil but fails to do so when the oculomotor nerve has been cut.

Summary

Observations upon the diameter of the pupil in the cat following preganglionic parasympathectomy, pre- and postganglionic sympathectomy, and combinations of these procedures indicate that inhibition of the third nerve is responsible not only for the reflex dilatation elicited by withdrawal of light and by painful stimulation, but also for the immediate dilatation conditioned by emotional excitement.

The sympathetic and the parasympathetic are opposed in their action upon the pupil. Under ordinary conditions sympathetic dilator tone is remarkably constant while third-nerve constriction is subject to extreme reflex modification. Consequently changes in the size of the pupil depend upon reflex variations in the activity of the oculomotor nerve. That sympathectomy effects a diminution in the extent and the rate of reflex dilatation demonstrates that in normal animals the dilatation caused by inhibition of the sphincter pupillae is augmented by the tonic contraction of the dilator muscle.

The effects of eserine upon the normal, the sympathectomized, the parasympathectomized and the sympathectomized-parasympathectomized pupil are compared and are plotted in Fig. 2.

Observations are reported which lead to the conclusion that nembutal depresses sympathetic activity.

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* Some seconds after strong sciatic stimulation which evoked struggling the parasympathectomized-eserinized pupil exhibited a slight dilatation. This effect could be reproduced by the administration of small doses of adrenalin. Similar delayed responses, which in our opinion are of humoral origin, have been noted by Ury and Gellhorn.

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MOVEMENTS ELICITED FROM PRECENTRAL GYRUS OF ADULT CHIMPANZEES BY STIMULATION WITH SINE WAVE CURRENTS*

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INTRODUCTION

TWENTY years after the classical paper of Leyton and Sherrington (1917) on the excitable cortex of the great apes was published, the task of stimulating the precentral gyri of three adult chimpanzees fell upon us. Although the chimpanzee has become a common laboratory animal, no recent attempt has been made to explore the whole precentral gyrus of this animal. Fulton and Keller (1932) reported results of occasional stimulation of this area (p. 97) in 7 chimpanzees (*Pan chimpanse*[=*satyrus*]) and Walker and Greene (1938) stimulated only the face area, in 4 animals (*Pan satyrus*). Leyton and Sherrington (1917) explored this gyrus in 22 chimpanzees (they mention two species, *Troglodytes niger* and *Troglodytes calvus;* Elliot's, 1913, synonyms, *Pan satyrus* and *Pan calvus*). Prior to that report all explorations of the "motor" cortex of this great ape were done in Sherrington's laboratory at Liverpool (Grünbaum and Sherrington, 1901, 11 animals; 1903, 5 animals; Graham Brown and Sherrington, 1912, 1913; and Graham Brown, 1914, 1916). The particular species used in those studies were also *Troglodytes niger* and *Troglodytes calvus.*

Three cytoarchitectonic studies of the distribution of Brodmann's areas 4 and 6 on the precentral gyrus of the chimpanzee have been published. First, that of Campbell (1905, p. 295) who studied one hemisphere each of two chimpanzees stimulated by Grünbaum and Sherrington in 1901 and 1902 (species given as *Anthropopithecus troglodytes*); second, that of Brodmann (1912) on one specimen of *Anthropopithecus troglodytes* (Elliot's, *Pan chimpanse*); and third, that of Bucy (1935) on 2 of the species, *Pan satyrus,* which had been used in Fulton's laboratory. Walker and Green related the results of their stimulation of the face area to its cytoarchitecture in 4 specimens of *Pan satyrus.* In each of these studies the distribution of areas 4 and 6 on the surface of the precentral gyrus was different. Whether this variation should be correlated with individual difference or with species difference or with the method used by the investigator cannot be determined at the present. Therefore, it becomes obligatory to correlate the results of electrical stimulation of each precentral gyrus with its own particular cytoarchitecture.

All of these investigators, with the exception of Walker and Green, used

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the faradic current from a laboratory inductorium as their source of electrical excitation. Since 1932 the present author has been using the sine wave current (see, Boynton and Hines, 1933; Hines and Boynton, 1940) for the exploration of the cerebral cortex of monkeys and common laboratory animals. Believing that the use of this current might uncover new facts not previously reported, these stimulations were undertaken.

MATERIAL AND METHOD

The three chimpanzees used in this study had been measured by Dr. A. H. Schultz. Dayton, a male (*Pan leucoprymnus*, Elliot, 1913; "all white") 15 years old, weighed 47.17 kg. on the day of stimulation of his precentral gyrus (May 26, 1938); Evo, a female (*Pan Kooloo-Kamba*, Elliot, 1913; "all black") 14 years old, weight 44.4 kg. (February 18, 1938); and Mae, also a female (*Pan chimpanse*, Elliot, 1913, "white, with brown nose") weighed 44.9 kg. (December 18, 1937).* They were therefore full-grown adults. Each in turn was caught in a small room, anesthetized by an ether spray. A special table was constructed so that the trunk was supported and the extremities hung free. Ether was given throughout the duration of the exploration by tracheal cannula. The anaesthesia was deep, so that residual palpable tone was minimal. Thus the results were restricted almost entirely in all probability to activation of the cortico-spinal tract.

Two types of exploration were done (i) a general exploration of the whole precentral gyrus with the 60 c.p.s. sine wave current, and (ii) an exploration of a single point with different frequencies of sine wave currents of 5 to 1440 c.p.s. The exploration of the precentral gyrus point by point should reveal the peculiarities of motor performance which characterize the chimpanzee, while that of a single point with various frequencies should establish the range of response of a small core of cortical neurones to electrical stimuli. The indifferent electrode was made of brass and kept in the rectum. The stigmatic electrode was a narrow platinum point (0.5 mm. in diameter) mounted on a slender spring, which protected the surface of the cortex from undue pressure.

Maps of the cortical blood vessels were drawn upon cilkoid, a thin transparent tissue so pliable that it will easily cling to the cortical surface. Upon these maps, the points stimulated were recorded. In the case of chimpanzee *M* (December 18, 1937, Fig. 1) a transverse row of points placed anterior to the precentral fissure were stimulated initially; this row was followed by others placed on lines which cut this fissure at right angles. This method of stimulation was intended to eliminate facilitation. In the remaining two, *E* (February 18, 1938, Fig. 2) and *D* (May 26, 1938, Fig. 3) the initial point stimulated was placed on the crest of the central fissure. Stimulation proceeded rostrally point by point placed on imaginary lines cutting the precentral gyrus horizontal to the long axis of the cerebral hemispheres. The paracentral lobule was stimulated in *M* and *D*. *E* died before the dorsal crest of the precentral gyrus was reached. No attempt was made to explore the anterior wall of the central fissure.

Among the observers† were well-qualified gross anatomists: consequently, the myology reported is, I hope, above reproach.

DATA

I. *Results of exploration of precentral gyrus with 60 c.p.s. sine wave current.*

A. *Area stimulated.* If the tracing of the cortical surface of these three precentral gyri be placed on cross section paper, the area stimulated on the surface of *M*'s brain was 816 sq. mm.; of that of *E*, 692 sq. mm.; and that of *D*, 918 sq. mm. The three topographi-

* Taxonomic study of chimpanzees since the time of Elliot's monograph on the primates (1913) indicates that the differing pigmentation of the face and extremities probably denote different racial groups rather than distinct species. All chimpanzees used hitherto in physiological work (save for Leyton and Sherrington's one specimen of *Pan calvus*, the bald-head chimpanzee) belong to the species, *Pan satyrus*. The adult animals used in Dr. Hines' study may be regarded as subspecies (Schwarz, *Ann. Mag. nat. Hist.*, 1934, *13* (10th ser.): 576) or varieties of *Pan satyrus*.—Ed.

† The writer wishes to thank Dr. Lewis H. Weed, Dr. E. P. Boynton, Mr. H. C. Raven and Dr. T. R. Forbes, for their able and efficient collaboration during these stimulations.

cal areas of face, arm and leg in these three brains were respectively, 196, 372 and 248 sq. mm.; 161, 362 and 169 sq. mm.; 284, 245 and 389 sq. mm. The total number of points stimulated in *M* was 122 in *E*, 154; and in *D*, 312. The distribution of this number in the three topographical regions for each animal was respectively, in the face region, 28, 40, and 103; in the arm region, 49, 80, and 83; and in the leg area, 45, 34, and 126. Of those stimulated in the face area in *M*, 2 were silent; in *E*, 3; and in *D*, 13. In the arm area of each chimpanzee, 1 point was silent and in the leg area in *M*, 3 were silent; in *E*, 1; and in *D*, 19. In *D*, 3 points gave movements of both arm and leg.

The density of distribution of the points in the three topographical regions were as follows:—in *M* in the face area 1 point per 7.0 sq. mm.; in the arm area, 1 per 7.5 sq. mm.; and in the leg area, 1 per 5.5 sq. mm., giving as an average 1 point per 6.6 sq. mm. In *E* the points were spaced more closely:—for the face, 1 per 4.0 sq. mm.; for the arm, 1 per 4.5 sq. mm.; and for that part of the leg area stimulated, 1 per 4.6 sq. mm.; giving an average spacing of 1 per 4.4 per sq. mm. In the case of *D*, the points were in each area more closely spaced than in *E*:—for the face area, 1 point per 2.7 sq. mm.; for the arm area, 1 per 2.9 per sq. mm.; and for the leg region, 1 per 3.0 per sq. mm., giving an average density of 1 point per 2.9 sq. mm.

This spacing of points was closer than Leyton and Sherrington used if the numbers placed upon certain of the precentral gyri indicate the actual number of points stimulated: for example, by count 134 were stimulated on the right precentral gyrus and 96 on the left of chimpanzee No. 6. The writers had hoped that by placing the stimulated points closer together, a greater variety of movements would be elicited, and that evidence of cortical activation of individual muscles as well as muscle groups would be obtained.

B. *Types of movement elicited.* The movements elicited by stimulation of the precentral gyrus fell naturally into two categories (i) simple or isolated movements: those made by the contraction of a single group of muscles and, in some instances, of a single or part of a single muscle, and (ii) compound movements: those made by the contraction of more than one group of muscles.

1. *Simple or isolated movements.* (a) *The face area.* Simple or isolated movements of muscles elicited by stimulation of the face area, innervated by the N. facialis, were as follows:—M. orbicularis oris (*M*, points F and I_2; *D*, pt. W_{12}), part of the M. platysma (*E*, pts. A_4, A_5, A_6, and E_1; *D*, pts. X_6 to X_{10}), M. risorius alone (*D*, pts. Y, Y_1, Y_4, Z, Z_1, a_3, and a_4) M. quadratus superior (*D*, pt. X_5) and the M. naso-frontalis (*D*, pt. W_6). Isolated movements of muscles innervated by the N. hypoglossus were obtained as follows:—M. longitudinalis superior (posterior fibers pt. I_3 in *M*, pts. b_1, e_5 in *D*; whole muscle, pts. C_2 to C_6, d, d_6, d_7, e, e_1, and h to h_3 in *D*, and pts. D and C_2 in *E*), vertical fibers of the tongue (pts. F_3, F_4, E in *E*; pt. f_5 in *D*), contralateral deviation of the tongue (pts. J, I in *M*, pt. F in *E*; pt. b_4 in *D*), slight contralateral movement of the tongue (pts. d_1 to d_5 in *D*), M. genioglossus (whole, pt. C in *E*, posterior part, pt. G_5 in *E*), and retraction of the tongue (pts. a_5, g_2, in *D*). Of the muscles innervated by the N. vagus, contraction of the contralateral M. glossopalatinus (pt. D_3 in *E*), of both Mm. palato-pharyngei (pts. b_2 and b_3 in *D*) was obtained. Contralateral deviation of the eyes (pt. F_1 in *M*), mastication (pt. G_1 in *M*) and opening of the mouth (pt. a_6 in *D*) were elicited only once each, and uncomplicated swallowing, twice only (pts. h_4, h_5, in *D*). Of the 90 reactive points in the face area of *D*, 48 give simple movements—11 of the 37 points in *E* and 7 of the 26 points in *M*. An increase in the number of points stimulated in the face area appeared to be related to an increase in the number of points giving single movements.

(*b*) *Remainder of precentral gyrus.* The reverse appeared in the case of the remainder of the precentral gyrus, for of the 189 reactive points in *D* only 91 gave isolated movements of a single muscle group; of the 112 in *E*, only 36; and of the 90 in *M*, only 40. Movements of the shoulder girdle itself occurred 17 times during the stimulation of the arm area of *D*, 3 times during that of *E* and twice in *M*. These movements were retraction, protraction, elevation and rotation (*D*), some form of adduction of the scapula (*E*), and abduction of the shoulder or contraction of trapezius giving retraction and elevation of the scapula (*M*).

Movements of the upper arm alone were noted more frequently than those of the thigh alone, as 12 to 7. But peculiarly enough 8 of the 12 of the upper arm and 5 of the 7 of the thigh occurred in a single animal (*M*). The frequency of occurrence of certain of these movements is of interest, for retraction of the upper extremity was observed 6 times, protraction 2 times (*D* only) and protraction of the leg 27 and retraction 8 times. Internal

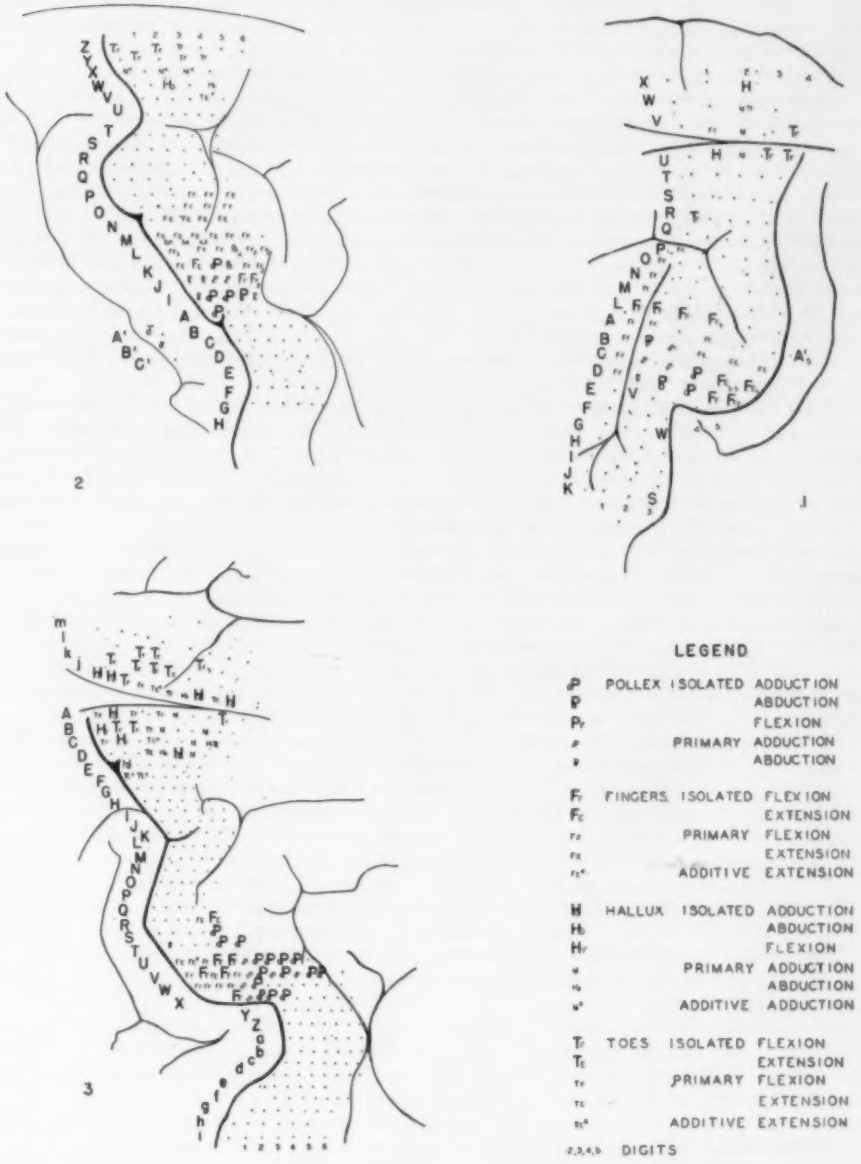


FIG. 1 to 3. These figures are pen and ink sketches of the cortical maps taken at the time of stimulation of each precentral gyrus. The legends are self-explanatory. Each dot marks the position of a reactive point. The first point stimulated is known by the letter of the row. The remaining points are identified consecutively by their number from the first point stimulated ×1.

Fig. 1. Map of the left precentral gyrus of chimpanzee *M*.

Fig. 2. Map of the right precentral gyrus of chimpanzee *E*.

Fig. 3. Map of the right precentral gyrus of chimpanzee *D*.

and external rotation of the upper extremity was seen 3 times each, but external rotation of the lower extremity, 14 times; and internal rotation, 3 times. Abduction of the arm to abduction of the leg were as 8 to 2, and adduction of the thigh was noted once only (*M*). And in *D*, 5 separate points gave contraction of the anterior fibers of the M. deltoideus Isolated flexion of the elbow was observed twice in *M* and 4 times in *E*; of the knee, 3 times in *D* and twice in *M*; extension of the knee, 6 times in *D*. Isolated flexion (3 pts.) and extension (2 pts.) of the ankle was obtained in *D*, but in both *E* (4 pts.) and *M* (1 pt.) only extension of the ankle. Similarly single extension (1 pt.) and flexion (1 pt.) of the wrist was found in *D*, and in *M* only flexion (1 pt.). Radial flexion of the wrist alone occurred in *D* only. No isolated supination or pronation was caused by stimulation of closely spaced points in the arm area of the male chimpanzee. Ten instances of simple pronation were noted in *E*, 2 in *M*, and but one instance of isolated supination in each of these animals. In all two points (B_6, E_1) on the cortex of *D* and one (S_2) on that of *M* caused isolated inversion of the ankle and three points (C_2, B_1, J_3) on the former cortical surface (*D*), isolated eversion.

The most frequently elicited movement of the fingers was adduction of the thumb (15 in *D*, 4 in *E*, and 3 in *M*). Isolated abduction of this member was obtained twice only (*E* and *M*). Simple adduction of the hallux occurred 6 times in *D* and twice in *M*, abduction twice only (*S* and *E*). A few isolated instances of movements of single fingers were produced, such as flexion of the index finger (J_5 in *E*; D_5 in *M*), adduction (C_5 in *M*) or flexion (L_5 in *M*) of the 5th finger. Isolated extension of the 5th toe was seen once (l_5 in *D*). Simple flexion of the 1st digit was also rare, occurring once of the thumb (B_1 in *M*) and once of the hallux (C_1 in *D*). Uncomplicated extension of the great toe was noted once only (B in *D*). Moreover, flexion of the lateral four fingers occurred more frequently than their extension, in ratios as follows:—6 to 1 in *D*, 2 to 1 in *E*, and 7 to 1 in *M*; and flexion of the lateral four toes to extension, in ratios of 9 to 1 in *D*; 2 to 0 in *E* and 4 to 0 in *M*.

The ratio of distribution of number of isolated movements of the lower extremity to that of the upper extremity was 43 to 48 (*D*), 8 to 28 (*E*, only part of leg area was explored), and 11 to 29 (*M*). Of these, the ratio of number of simple movements of digits to those of the proximal muscles elicited in the leg and in the arm areas were respectively as follows:—19 to 24, 22 to 26 (*D*): 4 to 4, 8 to 20 (*E*); and 4 to 7, 14 to 15 (*M*).

Therefore, the dominant isolated movements are retraction of the upper arm, protraction and external rotation of the thigh, flexion of the elbow, extension of the knee, pronation of the forearm, adduction of the first digits and flexion of the lateral 4. Isolated movements at the wrist and at the ankle did not show preference for any particular muscle group. Therefore, the 60 c.p.s. sine wave current can elicit contractions of single muscles or parts of muscles from the precentral gyrus of the adult chimpanzee.

(2) *Compound movements. Face area.* The compound movements which followed electrical stimulation of the face area fall naturally into three groups, namely: (i) those which result from the activation of more than one group of nuclei within a single motor nucleus, (ii) those which result from activation of more than one motor nucleus, and (iii) those which repeat a definite sequence of muscle contraction observed to be a part of the animal's reflex mechanisms.

Under the first group there are groups of muscles innervated by the N. facialis, the N. hypoglossus, and the N. vagus. Those innervated by the N. facialis were as follows:—retraction of both lips (*D*, *E*, and *M*), retraction of both lips and blink of the contralateral eyelid, retraction and depression of the lower lip, drawing in of the lower lip and closure of the contralateral eyelid (*M*), simultaneous contraction of Mm. auricularis and zygomaticus, of Mm. quadratus superior and zygomaticus. of Mm. risorius and orbicularis oris, of Mm. orbicularis oris and quadratus superior and of these two with the auricularis group (*D*).

Compound movements of the tongue produced by simultaneous innervation of more than one group of nuclei of the nucleus of the N. hyglossus were observed, namely:—retraction and contralateral deviation of the tongue (*D*, *E*, and *M*), elevation, retraction, and contralateral deviation of that organ (*M*), elevation and retraction (*D* and *E*), elevation and contralateral deviation plus wrinkling, and protrusion and contralateral deviation (*E*).

Contraction of muscles innervated only by the N. vagus was a rare occurrence, for depression of the pharyngeal arches and of the soft palates was caused but once (pt. g_6, in *D*).

In general when two cranial motor nuclei were activated simultaneously these were the nucleus hypoglossus and either the nucleus facialis or the nucleus vagus. All three nuclei were sometimes innervated. Movements of the lips and tongue were of frequent occurrence, for example, retraction of the contralateral corner of the mouth and contralateral deviation of the tongue, mass retraction of the corner of the mouth or of the lower lip (*E*) with retraction of the tongue (*M*), or contralateral deviation of the tongue and retraction of the lower lip (*E*). Movements of the tongue and of the pharyngeal arches were frequently obtained, especially in the male chimpanzee—such as retraction or elevation of the tongue and depression of the contralateral pharyngeal arch, and elevation of the tongue and bilateral depression or contraction of the pharyngeal arches. Retraction of the lip, eversion of the tongue and closure of the mouth were elicited once (pt. I, in *M*).

Contractions of the muscles of the contralatereal ear were associated with those of the tongue (pt. b_1, 0.28 mA. in *D*), or with those of the lips (mm. orbicularis, risorius, and auricularis, pt. Z_2, at 0.28 mA. in *D*), or with a mass retraction of the facial muscles in circular form (pt. F_3, 0.6 mA., in *M*); and closure of the contralateral eye (pts. E_1 and E_2, 0.6 mA. in *M*) was associated with movements of the contralateral facial muscles.

The third class of compound movements produced by stimulation of this region were those which followed a certain sequence, often seen in the animal's use of these muscles or in its reflex patterns of sequential movement. Such movements were of lips and tongue, or of mouth and tongue, or of the muscles of the pharynx and larynx, with and without those of the tongue—*i.e.*, movements used in manipulation of the food within the buccal cavitiy or in deglutition, as follows:—Closure of the lips followed by turning of the tongue to the right; eversion of the lower lip followed by retraction of the angle of the mouth, raising of the lower lip and deviation of the tongue to the right; elevation of the tongue and contralateral divergence followed by lowering of the soft palate and definite salivation; elevation of the uvula followed by swallowing (*M*); retraction and the lateral movement or elevation of the tongue followed by contraction of the palatine arches and elevation of the epiglottis; strong elevation and retraction of the epiglottis and marked contraction of the palatine arches; swallowing, followed by retraction of the tongue and closure of the mouth; and opening of the mouth and elevation of the tip of the tongue (*D*). Two rhythmical movements occurred when the face area of chimpanzee *E* was stimulated—retraction of the tongue and movements of the whole tongue followed by swallowing.

Arm and leg areas. For simplicity of analysis, movements elicited by stimulation of the arm and leg areas were classified as (i) those of the proximal muscles, *i.e.*, contractions of the muscles of the girdles or of those attached to the girdles, as (ii) those of muscles which move the knee or elbow, *i.e.*, of what shall be called the second joint; and as those which move the ankle or wrist, *i.e.*, of those which shall be called the third joint, as opposed (iii) to the twisting movements which supinate or pronate the lower arm or invert or evert the ankle, and as (iv) those which move the digits.

(i) *Proximal muscles.* Combinations of movements of shoulder girdle and of the upper arm seemed to follow certain patterns, such that elevation of the former was accompanied by retraction, internal rotation or abduction of the upper arm (*D* and *M*); retraction of the shoulder by adduction of the upper arm (*E*); and abduction of the shoulder by a circular movement of the upper arm (*M*). In one of these animals (*E*) the lower arm accompanied these movements: retraction of the shoulder was joined by flexion of the elbow and supination, and elevation by flexion of the elbow. In *D*, three consecutive points yielded retraction of the shoulder and contraction of the contralateral abdominal pressor muscles.

The combinations of movements of distal muscles with proximal muscles which followed upon electrical stimulation fell into two categories (a) those which began proximally and spread distally, and (b) those which began distally and spread proximally. Of the former, the most frequent type of co-innervation of the knee with protraction of the thigh was flexion (11 ×), for extension of that joint occurred only three times. With the rarer retraction of the thigh, extension of the knee was seen twice, and flexion 4 times. Flexion of the knee was the only movement to follow either external rotation (4 ×) or internal rotation (1 ×) of the thigh. Movement of distal muscles either accompanied or followed that of abduction or adduction of the thigh. Of the latter, in all responses of distally lying muscles which ended in some movement of the thigh, the included movement of the knee was flexion (4 in *M*, 7 in *E*, and 1 in *D*). Movements progressing from distal to proximal muscles, so frequently found to follow stimulation of the leg area, were seen but

twice in the total exploration of the arm areas of these three precentral gyri, as flexion of the fingers and elbow and internal rotation of the arm (pt. O_6, in *E*) and as extension of the fingers, flexion of the wrist and elbow and elevation of the shoulder and an undetermined movement of the ear (pt. P_1, in *M*).

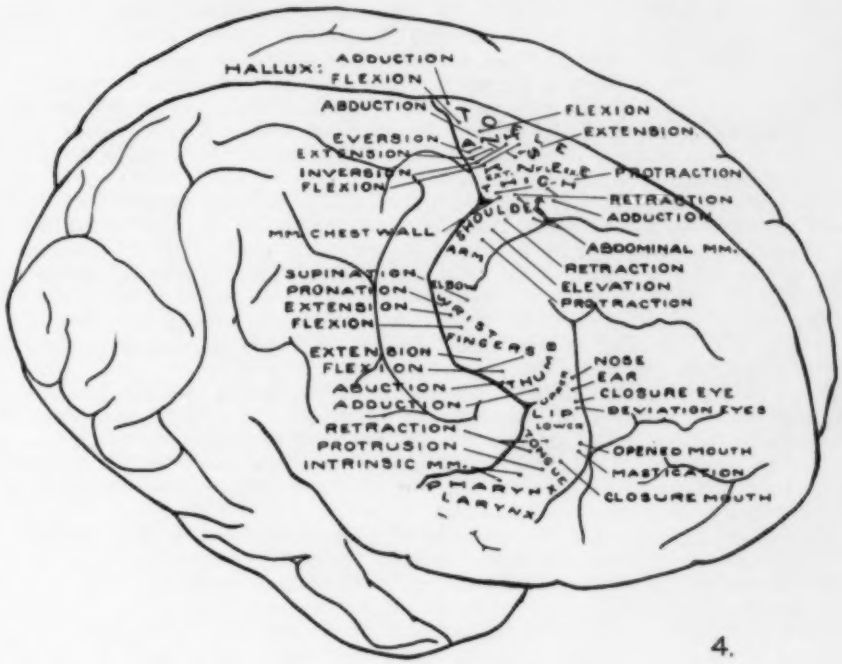
(ii) *Movements of second and third joints* of the extremities either singly or as co-innervations were produced from 41 points. However, co-innervations of these two joints only were relatively rare. Flexion of the wrist and of the elbow (pts. O_2 and N_2), and flexion of the ankle and of the knee (pt. T_3) were produced in *M* only; but extension of the ankle and flexion of the knee were obtained in both *D* (pts. M_5 and D_3) and in *M* (pt. T_2).

(iii) *Twisting movements.* The incidence of supination and pronation varied with the animal stimulated. In the co-innervations supination never occurred with extension of the elbow, only with flexion; and pronation only once with the former movement (*M*). Pronation was not obtained in a co-innervation which included movement of any muscle attached to the shoulder girdle; supination however was elicited twice as a part of movements involving such muscles in both *E* and *M*. The most frequently recurring movements with either supination or pronation were those of the fingers, extension or flexion. Such coinnervations might include or exclude movements of the wrist (either flexion or extension). Listing all combinations of movements of either pronators or supinators with those of the flexors or extensors of the fingers, in 22 movements out of a total of 25, the contractions of muscles of the fingers were primary in the sense of Leyton and Sherrington (1917).

In the tabulation of movements of inversion and eversion of the ankle, the fact that the leg area of chimpanzee *E* was not completely explored may account for the lack of appearance of inversion of the ankle. In the remaining two animals 10 points (*D*) and 3 points (*M*) gave inversion of the ankle. All but 2 points (D_6, C_7) in the former and 1 point (V_1) in the latter gave inversion as the initial movement. The additive movements obtained from all but 2 points (A_9, C_7) in *D* and 1 point (V_1) in *M* were those of the toes or of the ankle. However of these 3 points in which inversion of the ankle was produced as an additive movement, points D_6 and C_7 (*D*) yielded movements of the toes as the initial response and point V_1 (*M*), protraction of the thigh. Points A_9 (*D*) gave flexion of the toes and of the knee as additive; point C_7 (*D*), not only inversion of the ankle but also extension of that joint, flexion of the knee and protraction of the hip; and point V_1 (*M*), not only inversion of the ankle but also flexion of the knee.

Of the 5 points which yielded eversion of the ankle, 4 gave that movement as primary. The movement elicited from this 5th point (F_7 in *D*) was retraction of the hip, flexion of the knee and eversion of the ankle. From 3 (C_3, B_8 in *D*; W in *E*) of the remaining points the additive movements were those of other muscles of the ankle or of the toes; but point U_5 (*E*) produced bilateral contraction of the abdominal musculature ($1 > r$) as the secondary movement.

(iv) *Digits.* Tabulation of the movements of the digits produced by electrical stimulation of the precentral gyri of these three chimpanzees allowed a few generalizations. First, the variety of elicited movements was so great, that aside from simple adduction of the first digits and aside from flexion of all or of the 4 lateral toes, exact duplication of particular movements was not observed. Duplication of particular movements occurred only 4 times each in the exploration of the cortices of *M* and of *D*, and twice, in that of *E*. Aside from adduction of the first digit or flexion of the remaining 4, 131 different movements were listed in which some movement of the digits was observed to be either isolated or primary. Of the primary movements of the digits the more frequently recurring ones were adduction of thumb and flexion of the fingers, and adduction of the hallux and flexion of the toes. Primary adduction of the thumb was elicited from 9 points in *D*, from 8 points in *E* and from 3 points in *M*; primary adduction of the great toe, from 6 points in *D* and from 2 in *M*. Primary abduction of the thumb was obtained once each in *D* and *M*, and twice in *E*, while primary abduction of the great toe was even rarer, occurring once each in *D* and *E* and as a double movement of extension and abduction in *M*. Just as primary adduction of the first digit was elicited more frequently than primary abduction, so primary flexion of the lateral digits was caused more often than primary extension,—thus, ratios of primary flexion of the fingers to primary extension were as follows:—7 to 3 in *D*; 15 to 11 in *E*; and 9 to 6 in *M*. On the other hand primary flexion only of the toes was obtained, 3 times in *D* and *E*, and once in *M*. These movements of the digits occurred also as co-innervations. Adduction of the thumb was elicited with flexion of the fingers 19 times,



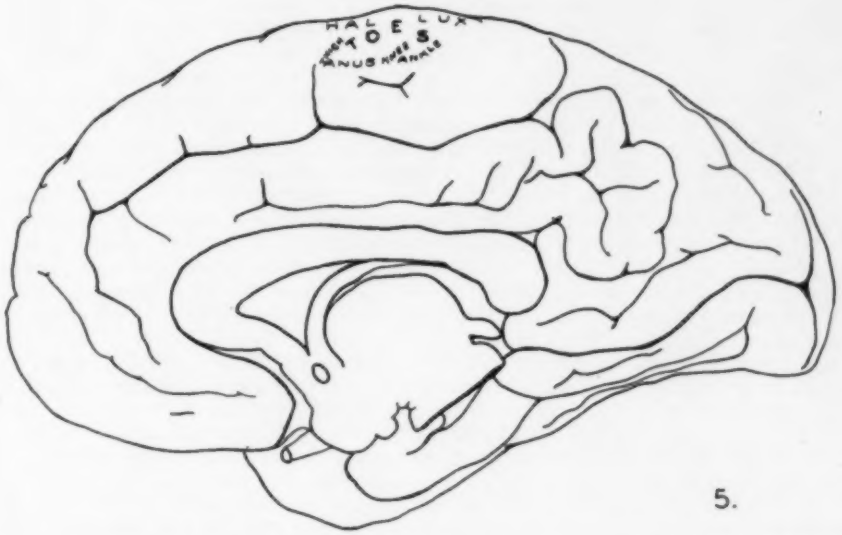


FIG. 4. Drawing of the lateral surface of the right cortex cerebri of a chimpanzee. The part of the body musculature responding to cortical stimulation is indicated as if projected upon the precentral gyrus. ×1.

FIG. 5. Drawing of the mid-sagittal section of the brain of a chimpanzee, showing the part of the body musculature which responded when the paracentral lobule was stimulated. ×1.

but with extension only once (pt. I_4 in *E*); abduction of the thumb, with extension of the fingers 3 times, with flexion twice. Similarly, adduction of the hallux was observed to occur with flexion of the toes 19 times, with extension, not even once; but with abduction of the hallux, flexion of the toes happened twice only and extension, 3 times. Therefore even in the compound movements abduction of the first digit was rarer than adduction and extension of the lateral 4 digits was rarer than their flexion. Also adduction of the first digit tended to occur more often with flexion of the lateral four; and abduction of the first, with extension of the lateral four digits.

The movements, secondary to primary flexion or to primary extension of the fingers, seemed to follow certain patterns. Although primary flexion or extension of the fingers was followed by extension or by flexion of the wrist, the proportion of occurrence of extension of the wrist to flexion of the wrist was greater when the primary movement was extension of the fingers than when it was flexion (7 to 5) and less when the primary movement was flexion of the fingers (5 to 11). The total number of primary flexions of the digits was 25 in all three cortices; of primary extensions, 18. Only once was the upper arm seen to participate in this group of additive movements (pt. O_6 in *E*).

Seven different combinations of movements were observed to follow primary flexion of the toes (all of the lateral 4). Among these additive (*i.e.*, any movement not primary) movements extension of the ankle was noted 5 times; flexion of the ankle, not at all; flexion of the knee, once only; and movements of the thigh on the hip twice,—once as a combined retraction and lateral rotation, and once as protraction, accompanied by contraction of the left abdominal musculature.

Movements of the digits also occurred as additive movements. For the first digits, such occurrences were relatively rare. Six such instances of additive adduction of the thumb followed primary flexion of the fingers, while the one instance of secondary abduction of the thumb was an example of deviation, beginning with pronation. No such complete uniformity was found when adduction of the hallux was elicited as additive, for movement of the ankle (extension or inversion) was noted in 6 of the 8 instances. These exceptions were flexion of the lateral 4 toes (pt. W_2 in *M*) and flexion of the knee (U_2, in *M*). Abduction of the hallux was seen among the movements elicited by stimulation of the precentral gyrus of *D* only. The primary movements here were extension of the 4 lateral toes, extension of the hallux and inversion of the ankle (2 points).

A comparison of the frequency of occurrence of secondary extension of fingers with that of secondary flexion shows that additive flexion of the fingers was definitely rarer than additive extension, for 14 instances of the former occurred and only 5 of the latter. The 5 different varieties of initial or primary movements which preceded extension of the fingers were distributed as follows:—extension (2×) or flexion (5×) or ulnar flexion (1×) of the wrist, pronation of the forearm (5×) and flexion of the elbow (1×). In each of the 5 instances in which flexion of the fingers was secondary, the primary movement was different,—flexion of the elbow, flexion or extension of the wrist, contraction of the M. brachii radialis and pronation. The distribution of these secondary movements of the fingers in the various animals was respectively as follows:—extension 1 and flexion 3 in *D*; 6 and 10 in *E*; and 5 and 2 in *M*. On the other hand additive flexion of the toes occurred 7 times and additive extension, 5 times. Five of the former and all of the latter followed an initial movement of the ankle. The remaining two additive flexion of the toes followed primary protraction of the thigh or flexion of the knee.

Only certain of the co-innervations of thumb and of fingers were suggestive of use patterns. It is easy so to interpret adduction of the thumb and flexion of the lateral 3 fingers (pt. V_5 in *D*) or of the index finger (V_7, V_8, in *D*) or of the index and 3rd finger (W_4 in *D*; I_4 in *E*), or of the 3rd and 4th fingers (W_3 in *D*), or of apposition of the thumb to the fingers in flexion (K_3 in *E*) or to the 4th finger (L_4 in *E*). But serial flexions (2nd to 5th fingers, J_4 in *E*; 2 to 4th, D_4 in *M*) or extensions (5th then 4th fingers C_5, 3rd, 4th and 5th fingers, C_4 in *M*) of the fingers suggest not use patterns as such but rather the anatomical prerequisite for the ability to flex or extend the digits in different degrees in use. Similarly the simultaneous abduction of the thumb and extension of the 2nd finger (J_1, at the 1st and 2nd joints J, *M*) could be so interpreted. There were only a few movements of the toes which could be considered cooperative, such as flexion of these toes and abduction of the hallux (J_2, J_5, *D*) and the reverse order (V_2, V_3, in *M*), flexion of toes (2 to 4) followed by that of the hallux (B_1 in *D*) or flexion of all 4 lateral toes plus flexion and adduction of the great toe (B_2 in *D*).

Again certain movements remained dominant, whether produced as isolated or compound. Retraction of the upper arm always exceeded protraction; external rotation of the thigh, internal rotation; pronation of the forearm, supination; and extension and inversion of the ankle, its flexion and eversion, respectively. Isolated or primary flexion of the fingers outran isolated or primary extension of the fingers; but additive flexion was rarer than additive extension. On the other hand certain movements were dominant when elicited either as isolated or as co-innervations. Isolated retraction of the thigh was produced more often than isolated protraction, but the total number of protractions exceeded the total number of retractions. Isolated extension of the knee occurred more frequently than isolated flexion but co-innervations including flexion of the knee outnumbered co-innervations including extension.

Moreover, certain compound movements gave opportunity for interpretation of the capacity of the "motor" cortex; for contractions of some muscles tended to occur only in certain co-innervations. Co-innervations of the digital muscles found adduction of the first associated with flexion of the others, and abduction of the first, with extension of the remaining. Although either flexion or extension of the knee followed either retraction or protraction of the thigh, only flexion of the knee followed internal or external rotation. Supination and pronation were more often primary to contraction of proximally lying muscles, but inversion and eversion of the ankle to contraction of distally lying muscles (movements of the toes). However, when the first 3 of these movements were additive, the common initial movement was of the digits. As additive movements, flexion of the fingers was rarer than extension, but extension of the toes, rarer than their flexion. The spread of contraction from distal muscles to proximal muscles were more frequent and more extensive as responses to stimulation of the leg area than of the arm area. But the variety of the co-innervations elicited from the arm area of the chimpanzee cortex was greater than those from the leg area.

C. *Movements of extremities and of trunk not obtained.* Only a few movements of the possible theoretical ones were not elicited by stimulation of the precentral gyrus of these three chimpanzees. No movements of the head on the neck, no extension at the elbow and no adduction of the arm were seen at any time. In *M* no radial or ulnar flexion nor extension of the wrist, no protraction or external rotation of the upper arm and no extension of the knee were obtained. In *E*, however, only protraction and internal rotation of the upper arm, flexion of the ankle, extension of the knee medial rotation and adduction of the thigh were missing, while in *D* only internal rotation of the upper arm.

D. *Movements infrequently obtained.* (a) *Bilateral movements* were produced and in general were those of the abdominal musculature. Stimulation of *D*'s cortex yielded from certain points the following:—contraction of the abdominal pressor musculature on both sides followed by retraction of the left thigh (contralateral), flexion of the left knee and flexion of the right knee (pt. J, 0.3 mA.), retraction of the left thigh and abduction of the right thigh (pt, K, 0.3 mA.), contraction of the abdominal pressor musculature (pts. M_4, 0.4 mA. and M_5, 0.6 mA.), protraction of right thigh, extension of the right knee and a slight tremour and undetermined movement in the left knee (pt. I_1, 0.3 mA.). Repeated stimulation of point K gave similar results, for with a similar strength of current and with a slight decrease (0.27 mA.) a similar movement was obtained. But when the last strength of current was again applied, not only was retraction of the left thigh and abduction of the right obtained but slight retraction as well.

E's cortex proved particularly rich in bilateral responses of the abdominal musculature. The contraction of these muscles on the left was greater than the right and followed or preceded eversion of the foot (pt. U_5, 1.5 mA.), extension of the ankle (pt. W_5, 1.0 mA.), protraction of the leg, retraction of the arm (pt. T_5, 2.0 mA.), and protraction leg, flexion knee, extension ankle, spreading of toes and external rotation and abduction of the upper arm (pt. U_1, 1.0 mA.).

(b) *Unusual responses. Changes in respiratory movements* were observed in all 3 animals. Sudden and tremendous over-ventilation of the lungs followed immediately upon the stimulation of two points (a_8, 0.27 mA., and i_6, 0.6 mA.) anterior to the inferior precentral fissure and anterio-rostrally placed on the precentral gyrus of *D*. The other changes in respiration appeared to accompany movements of the chest wall itself and were located near the leg-arm interregional border. Point K_1 (0.27 mA.) on *D*'s precentral gyrus gave a change in respiration by contracting the anterior wall of the thoracic cage; and the first stimulation like that of K_1, of point X_4 (*E*'s cortex) elicited a deepening of the respira-

tory movements after a slight inhibition. A second stimulation of this same point (current strength similar, 2.0 mA.) added, to this delay and deepening of the respiratory movements, protraction of the thigh, flexion of the knee, and extension of the ankle. In *M* the initial stimulation of point O_3 (0.6 mA.) produced abduction of the shoulder girdle. Repetition of stimulation of this point (0.8 mA.) was followed not only by abduction of the shoulder and circumduction, but also by a respiratory spasm.

Vocalization was obtained as a single result upon the second stimulation of point E_1 (0.8 mA.) in *M*, and a light whistle followed wrinkling of the lips in the midline and that of the corner of the mouth when point G_3 (0.6 mA.) was touched with 0.6 mA. of the sine wave current. In this same animal the second stimulation of point K_3 (0.4 mA.) caused not only an elevation and deviation of the tongue to the right, and a lowering of the soft palate, but also an increase in salivation.

Well within the face area of *E*'s precentral gyrus, stimulation of point C_1 (1.0 mA.) yielded not only deviation of the tongue to the left and slight retraction of the lower lip, but also retraction of the contralateral arm accompanied by flexion of the wrist.

E. *Localization of points on precentral gyrus from which movements were elicited.* The three topographical regions were definitely outlined on the surface of the precentral gyrus of each of these three chimpanzees. A line drawn from the caudal spur of the superior precentral fissure cutting the central fissure through its dorsal rostral curvature formed the interregional leg-arm boundary. A ventrally placed line cutting the inferior precentral fissure and the central fissure about the middle of its sharpest ventro-rostral curvature separated the arm and face regions. On *M*'s cortex these two lines were parallel to the horizontal axis of the cerebral hemispheres. On both *E*'s and *D*'s cortices these separating lines were irregular.

Within the face area stimulated in these three brains the greatest surface responded with tongue movements and the least, with muscles innervated by the tenth cranial nerve (nucleus ambiguus portion). The area which yielded movements of the facial muscles could be divided into 3 zones,—a dorsal for movements of the upper lip, a ventral for those of the lower lip, and a rostral for movements of the muscles of the nose, ear and eyelid. Movements of the tongue musculature were obtained in three fairly distinct concentric zones running across the precentral gyrus, dorso-rostrally to ventro-caudally, giving respectively, retraction, protrusion and movements of intrinsic muscles. Anteriorly, both opening and closure of the mouth were located. Such a cortical pattern suggests direct neuronal relationships with individual nuclei of the nucleus facialis and the nucleus hypoglossus.

Within the arm area the most extensive surface was assigned to movements of the thumb. The thumb area adjoined the face area on its dorsal border. The points which gave isolated or primary movements of the flexors of the fingers were found close in cortical space to those which responded with movements of the thumb. In general, the flexor points were located more ventral and rostral on concentric arcs than were those which yielded isolated or primary movements of extension of the fingers. No exact localization for the movements of individual fingers could be discovered in these results. However, instead of the ladder-like representation of the digits given for the human (Foerster, 1936), movements of the 5th finger and those of the 2nd were sometimes elicited from neighboring points. Reading the movements produced from points which lie on the caudal division of the precentral gyrus, the somatotopical distribution was substantiated, for passing from the more ventrally to more dorsally lying points the muscles responding climbed the arm. However, if the movements caused by stimulating the more rostral division of the precentral gyrus be projected upon the points from which they were obtained, it was discovered that about midway on the rostral border the representation of the more proximal muscles curves ventrally to meet that of the more distal muscles curving dorsally.

In the leg area abduction of the hallux was observed as a frequent co-innervation with extension of the toes, adduction with flexion. But adduction of the hallux and flexion of the toes were frequently produced separately. The points from which the former movements were obtained were located more ventrally and on the lateral surface of the precentral gyrus. The latter movements were elicited from more dorsally lying points on the precentral gyrus or from points on the paracentral lobule. In *E*, no isolated or primary adduction of the hallux was obtained, only abduction of that digit. The area which in the other two cortices yielded isolated adduction of the hallux was not stimulated. In the other two cortices, the surface area which gave primary or isolated adduction of the hallux or

flexion of the toes was greater than that which gave abduction or extension. Aside from this particular localization of extension and flexion of the digits, the proximal muscles of the leg were localized more ventrally on the lateral surface of the precentral gyrus than were the distal muscles. However, the most rostrally lying points brought the representation of the distal muscles closer to that of the proximal muscles.

On the paracentral lobule of *M* all movements of the toes were those of flexion; of *D*, 10 of the 29 reactive points gave flexion of the toes, and 2, extension. Seven points (*D*) gave adduction of the hallux and 1 point, abduction. Three points of the 18 reactive ones found on this part of the motor cortex of *M* gave adduction of the hallux. Flexion of the knee and protraction of the thigh, extension and inversion of the ankle were elicited from both, but eversion from *M* only and internal rotation of the thigh and flexion of the ankle from *D* only. Contraction of the anal sphincter was obtained from the more rostral and ventral points of this lobule in both. In *M* this movement occurred also as a co-innervation, with extension of this ankle; in *D*, as a co-innervation with protraction of the thigh. However, in *D* the latter movement also occurred from the two most ventro-rostral points as a co-innervation with contraction of the levator ani.

Movements which involved muscles acting at 3 or more joints and produced by threshold stimuli were located on the anterior border of the arm or leg regions. Similar movements, however, were caused by supraliminal stimuli of more caudally lying points.

The bilateral movements observed in *D* and *E* were all obtained by the stimulation of points lying in the vicinity of the leg-arm inter-regional borders.

No ladder-like representation of the digits on the precentral gyrus was uncovered in any one of these stimulations. As noted in the previous section, the only movements of individual digits found, were those of the index and little fingers. Such movements were obtained from points as widely separated as the whole width of the "motor" cortex itself. For example, flexion of the index finger was elicited from point D_5 in *M* (caudal), from points J_5, K_5, L_5 and L_6 (rostral) in *E*; and flexion of the 5th finger, from L_3 (midway) in *M*, and from L (caudal) in *E*.

The change in respiration which could be allocated to changes in rhythm of movement of the chest wall were found in *E* (pt. X_4) rostrally in the leg area, and in *D* (pt. K_1) caudally in the leg area. The over-ventilation of the lungs obtained twice in *D* was found outside the precentral gyrus (pt. a_8) and on the rostral border (pt. i_6). The vocalization (pt. E_1) and the light whistle (G_3) elicited in *M* were obtained dorsally on the face area.

F. *Question of threshold of "motor" cortex.* Projection of the thresholds of the points stimulated upon each cortex in turn showed, (i) that whatever the average threshold for the particular cortex, the greatest number of low threshold points were found in the face area, (ii) that a particular cortex appeared consistent, maintaining throughout the experiment a characteristic threshold, and (iii) the greater number of points having similar thresholds were found to cluster about similar values for both the leg and arm areas in each animal.

Face area. On *E*'s face area 26 out of 37 reactive points had a threshold of 0.7 mA.; on *M*'s face area, 5 points had a threshold of 0.4 mA., 7 of 0.6 mA., out of 26 reactive points; and on *D*'s face area, of the 90 reactive points, 21 responded to 0.22 mA. of current, 28 to 0.28 mA., and 21 to 0.36 mA.

Arm area. Similarly in the arm area of these respective cortices, 31 points yielded movement to 0.7 mA. of current and 36 to 1.0 ma. of the 79 reactive points on *E*'s cortex; 17 points to 0.6 mA. and 11 to 0.8 mA. out of 48 reactive points stimulated in this region of *M*'s precentral gyrus; and 35 points to 0.36 mA. and 13 to 0.4 mA. out of 82 reactive points in the upper extremity area of *D*.

Leg area. Of the 33 reactive points stimulated on the leg area of *E*, 10 yielded movements to 0.7 mA. of the 60 c.p.s. sine wave current and 17 to 1.0 mA.; of the 42 reactive points on this region of *M*'s cortex, 10 gave movements when stimulated with 0.6 mA. and 12 with 0.8 mA.; and of the 104 reactive points on *D*'s leg area, 30 points responded to 0.36 mA. and 16 points to 0.4 mA.

The thresholds of points which were lower than the above had the following values and distribution:—for *E*'s face area, 1 point at 0.5 mA.; for *M*'s face area 3 points at 0.2 mA., for her arm area 2 points at 0.3 mA., 6 at 0.4 mA., and 2 at 0.5 mA.; and for her leg area, 2 points 0.3 mA., and 4 at 0.4 mA.; and for *D*'s face area, 21 points at 0.22 mA., for his arm area 2 points at 0.22 and 0.24 mA. each and 8 at 0.32 mA., and for his leg area, 2 points at 0.27 mA., 17 points at 0.3 mA., and 4 at 0.33 mA. The low threshold points on

the face area yielded movements of single muscles about the mouth or of the tongue. All of these points except certain ones in *D* (12 points *i.e.*, pts. X_6 to X_{10} and pts. W_2 to W_{12}) were found caudally on the gyrus in the dorsal region of the face area. The low threshold points of the arm area were also located caudally in the precentral gyrus of *E* and of *M*. All of these low threshold points, except 4 (pts. V_8 to V_{11}, 0.32 mA.) which were located ventrally and rostrally, were also distributed caudally on *D*'s arm area as well. The low threshold points on *D*'s arm area yielded either isolated or primary movements of the fingers and of those on *M*'s middle precentral gyrus, 6 out of 10 had caused movements either of the thumb or of the fingers. In the leg area the low threshold points were found distributed on the caudal part of the precentral gyrus. However, the movements which these particular points produced were frequently (not always) isolated movements of a part of the musculature of the lower extremity; but unlike the low threshold points of the arm area which yielded movement of distal muscles, those of this leg were unconfined to particularly placed muscles.

The high threshold points in the face area were located on the anterior border in *E* (g_5, 1.5 mA.) beyond the inferior precentral fissure in *M* (1.6 mA., pts. I, J, K; 2.3 mA., pts. H, G, F, E) and either on the anterior (0.6 mA., pt. W_6; 0.48 mA., pts. X_8 and Z_6; 0.4 mA., pts. g_6 and g_7) or on the ventral (0.6 mA. pts. i to i_6; 0.4 mA., pts. h to h_5) border in *D*. Again without exception the high threshold points in the arm areas of these three cortices were discovered on the anterior border or on the rostral portion of the precentral gyrus (in *E*, 1.5 mA., pts. K_5, M_6, O_5, O_6, Q_7; 2.0 mA. pts. N_4, P_6, R_5, T_5: in *M*, 1.2 mA., pts. D, N, O; 1.4 mA. pt. L and 1.8 mA., pt. M; in *D*, 0.8 mA., pt. T_5, R_4 to R_6, P_4, N_4; 0.6 mA., pts. S_4, P_3, M_5). The high threshold points of the leg area were localized in all three chimpanzees on the rostral border of the precentral gyrus and in *M* and *D* on the ventral border of the paracentral lobule as well (in *E*, 1.2 mA., pt. Y_4; 1.5 mA., pts. U_5, U_6, Z_6; and 2.0 mA., pts. X_4 and W_4; in *M*, 1.2 mA., pts. Q, T, U, V, W, X, X_1; and 2.0 mA., pt. X_2: and in *D*, 0.8 mA., pts. E_4, A_5, M_2 to M_{11}, I_{10}; 0.9 mA., pts. I_4, H_5, G_5, F_5; and 1.0 mA., pts. D_7, C_7).

In general then, the elicitation of movement from the more anterior edge of the precentral gyrus required a stronger current than from points lying 1 or 2 mm. posteriorly. This was found to be true whether the initial order of stimulation was transversely across the rostral crest of the inferior precentral fissure as in *M*, or whether each row of points was explored separately beginning on the anterior crest of the central fissure as in *D* and *E*. Although in the latter two cortices facilitation must have played a part, nevertheless, the abruptness with which the threshold was raised on the anterior border of the gyrus appeared to indicate that the edge of area 4 had been reached.

No generalization can be made about the type of movement elicited from these several high threshold points, except to say that the movements were rarely simple isolated movements at single joints. Often these movements were widespread co-innervations involving synergic groups of muscles located either proximally or distally or throughout a single extremity.

G. *Reversal; deviation; facilitation.* Of the 153 points (total all 3 cortices) restimulated with an intensity of current at threshold or above, only 2 points (K_2 and S_2 in *M*'s cortex) showed deviation of response. Stimulation of K_2 with 0.4 mA. elicited a ripple divergence of the tongue to the right; repetition (no change in current strength) elicited elevation of the uvula and narrowing of the fauces. Point S_2 yielded on 1st stimulation (0.8 mA.) contraction of the hamstring muscles; on 2nd (1.0 mA.), contraction of the M. biceps femoris; and on 3rd (1.2 mA.), inversion of the foot. Simple reversal, although not as infrequent, was also rare. In these three cortices the reversal common to all was that of abduction or adduction of the first digit. On *E*'s cortex, 0.7 mA. caused abduction of the thumb (pt. I_3); followed by 1.0 mA. the stimulation gave adduction of the thumb. Stimulation of point D_2 in *M*'s cortex with (i) 0.6 mA. yielded abduction of the thumb, (ii) 0.4 mA. gave no movement, and (iii) 0.5 mA. adduction of the thumb. In this same animal 0.6 mA. current elicited, from point U_1, flexion and adduction of the hallux, and 0.4 mA., extension and abduction of the hallux. The initial stimulus of point A, (chimpanzee *D*) produced adduction of the hallux (0.6 mA.); the 2nd stimulus (0.4 mA.) gave abduction followed by adduction.

Facilitation was obtained with great ease in all 3 cortices with a series of stimuli of increasing intensity. In the case of *M*, 3 points yielded facilitation when stimulated with a series of decreasing intensities of current. One example will suffice. Point S_1 gave

(i) with 0.8 mA. of current, flexion of the knee and protraction of the thigh, (ii) with 0.6 mA., the same movement plus lateral rotation of the thigh, and (iii) with 0.4 mA., the movement elicited with 0.6 mA. plus extension of the foot.

Centripetal individuation. On the other hand stimulation of a single point (all 3 cortices) with a series of decreasing strengths of current elicited a decrease in the number of muscles contracting or in the number of fibers within a given muscle. Two examples will suffice to illustrate this phenomenon which Boynton and Hines described in 1933. (i) With 0.32 mA. of current applied to point W_3 (chimpanzee *D*) there resulted flexion of the 4 lateral fingers, adduction of the thumb, flexion of the wrist, and supination of the forearm, (ii) with 0.28 mA., adduction of the thumb and flexion of the 3rd and 4th fingers, and (iii) with 0.22 mA., adduction of the thumb and slight flexion of these fingers. Point S_3 (chimpanzee *M*) when stimulated (i) with 0.8 mA. produced protraction of the thigh and flexion of the knee, (ii) with 0.6 mA., slight flexion of the knee, and (iii) with 0.4 mA., a twitch of the hamstring muscles, not sufficient to move the knee.

The occurrence of these 4 phenomena will be discussed further when the results of stimulation of single points with different frequencies of the sine wave current are presented.

H. *Results of stimulation of points outside precentral gyrus.* (a) *The postcentral gyrus.* In order to determine whether or not stimulation with this current required the process of facilitation to make the postcentral gyrus reactive, the first point on *E*'s cortex touched with the stigmatic electrode was located immediately anterior to the inferior limb of the fissura postcentralis on the level of point A as given in precentral gryus. This point A′ (Fig. 2) yielded adduction of the thumb (1.0 mA.). The next point below A′, B′, gave adduction of the thumb, flexion of the wrist, supination and slight flexion at the elbow (1.0 mA.). Strangely, point A'_1, placed 2 mm. anterior to A′ gave nothing even with 1.5 or with 2.0 mA., nor did point C′, 2 mm. ventral to B′ with 1.2 mA.

After the exploration of the whole of the precentral gyrus and of one point with certain frequencies, a point opposite A_5 on the precentral gyrus of *M* was stimulated on the postcentral gyrus, point A'_5. Point A_5 had not been stimulated for 4 hours and 45 min. Point A'_5 gave (2.0 mA.) flexion of the fingers and pronation.

(b) *Area 6.* All points initially stimulated in *M*'s cortex from point A through point O lay on the anterior crest of the inferior precentral fissure. The results of these stimulations were mentioned above.

After the complete exploration of *M*'s "motor" cortex and of one point (D_2) with various frequencies of the sine wave current, 3 points widely separated but well within area 6 were stimulated. Point 6A (2.0 mA.), gave a slow clonic protraction of the thigh; point 6B (2.0 mA.), a slow clonic protraction of the thigh; and point 6C (1.0 mA.), flexion at the knee, protraction of the thigh and extension of the ankle. This movement was of wide amplitude and clonic. Restimulation of this point with 2.0 mA. added flexion of the toes and changed the clonic aspect of the movement to that of a beating movement.

At a similar period in the experiment and over a similar area, 7 points were stimulated in *D*'s area 6, the first 4 points with 1.0 mA. of the 60 c.p.s. sine wave current and the last with 0.8 mA. These movements were as follows:—points 6a and 6b a jerky protraction of the thigh; 6c, a similar movement but followed by repeated tonic contractions of the protractors; 6d, a jerky protraction of the thigh and flexion of the knee; 6d, repeated with 0.8 mA. yielded retraction at the shoulder and flexion of the elbow; 6e, nothing; 6f, retraction and external rotation at the shoulder and slight flexion of the elbow; and 6g, external rotation of the upper arm.

II. *Results of stimulation of single point with different frequencies (5 c.p.s. to 1440 c.p.s.) of sine wave current (Fig. 6).*

After completion of the exploration of the surface of the precentral gyrus with the 60 c.p.s. sine wave current, point D_2 on that of *M* and point C on that of *D* were chosen for exploration with various frequencies of the sine wave current ranging from 5 to 1440 c.p.s. The order of stimulation of these two points with these frequencies was similar. The general level of the intensities of the 60 c.p.s. sine wave current found liminal for the surface of the "motor" cortex of *M* was higher than that for this portion of *D*'s cortex. Similarly, the effective strength of the frequencies applied to point D_2 on *M*'s cortex was higher than the effective intensities of similar frequencies applied to point C on *D*'s cortex. This minimum threshold frequency may be called the optimum frequency. Plotting the threshold for movement against the logarithm of the frequency produced the curve in

Fig. 6. The gradient of the curve for frequencies below the optimum frequency was steeper than that for those above. For both point D_2 and point C on these two cortices the optimum frequency (of those used) was 90 c.p.s. (0.13 mA., pt. C: 0.25, pt. D_2). In each exploration the frequencies which approached the minimum effective intensity of the optimum frequency were 120, 180, and 240 c.p.s. (0.2 mA., for each of these 3 for pt. C: 0.4 mA., for the 1st. 2, and 0.5 mA. for the last for pt. D_2).

Comparable rises in the intensity of the effective current at certain frequencies were noted. The first comparable rise in the intensity of the thresholds of these 2 points were

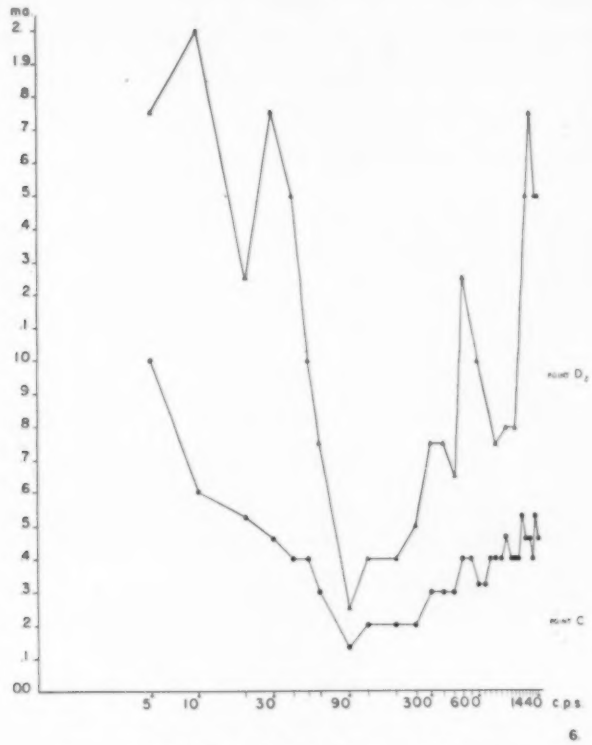


FIG. 6. The liminal intensities of the sinusoidal currents (5 to 1440 c.p.s.) giving movement were plotted in semilogarithmic coordinates. The upper curve (labeled point D_2) was found on *M*'s precentral gyrus; the lower curve (labelled point C), on *D*'s precentral gyrus.

found at 300 c.p.s. (0.33 mA. for pt. C and 0.75 mA. for pt. D_2) and another at 480 c.p.s. (0.4 mA. pt. C: 1.25 mA., pt. D_2). Both fell with stimulation with 600 c.p.s. (0.33 mA., pt. C: 1.00 mA., pt. D_2), and were higher again together with 840 c.p.s. (0.4 mA. pt. C: 1.25 mA., pt. D_2). They rose together with 1140 c.p.s. (0.46 mA., pt. C: 1.5 mA., pt. D_2) and with 1260 c.p.s. (0.46 mA., pt. C: 1.75 mA., pt. D_2). With 1380 c.p.s. the threshold for the movement from point C was higher (i.e., 0.53 mA.) and for point D_2 lower (i.e., 1.5 mA.), and with 1440 c.p.s. the threshold was lower again (0.46 mA.) for point C, but for point D_2, similar (1.5 mA.).

The intensity of the stimulating frequency which produced the movement increased consistently with the frequencies less than 90 c.p.s. for point C on *D*'s cortex, (0.33 mA., 60 c.p.s.; 0.4 mA., 50 and 40 c.p.s.; 0.46 mA., 30 c.p.s.; 0.50 mA., 20 c.p.s.; 0.6 mA., 10 c.p.s.; and 1.0 mA., 5 c.p.s.) but for point D_2 on the cortex of *M*, the effective intensity for

30 c.p.s. was greater than that of 20 c.p.s., and the 10 c.p.s., greater than 5 c.p.s. (0.75 mA., 60 c.p.s.; 1.0 mA., 50 c.p.s.; 1.5 mA., 40 c.p.s.; 1.75 mA., 30 c.p.s.; 1.25 mA., 20 c.p.s.; 2.00 mA., 10 c.p.s.; 1.75 mA., 5 c.p.s.).

Stimulation of point C produced extension of the ankle with each cycle used with the exception of 360 c.p.s. Stimulation of point D_2 produced adduction of thumb with each cycle used with the exception of 10, 360, and 1260 c.p.s. Strangely enough the stimulation with the 360 c.p.s. on each cortex produced deviation—point C gave abduction of all toes and extension of the hallux and point D_2 yielded flexion of all fingers and flexion of the elbow. Both 10 and 1260 c.p.s. on point D_2 produced a deviation—flexion of the thumb rather than adduction. The liminal stimulus for each cycle used did not always give the simple movement of extension of ankle (point C) or of adduction of the thumb (point D_2). Co-innervations were elicited. Those accompanying extension of the ankle were most frequently another movement of the ankle (eversion, 8 ×; inversion, 6 ×) and those with adduction of the thumb were movements of the forearm (supination 9 ×, pronation 1 ×) or of the wrist (radial, 4 ×, or ulnar 1 × flexion). Extension of the toes was observed five times and flexion of the toes once as co-innervation with extension of the ankle (point C) and five times flexion of the fingers and twice extension and once flexion of the index finger were seen as co-innervations with adduction of the thumb (point D_2).

Point C was stimulated with a supraliminal strength (0.66 mA.) kept constant for each of the 31 cycles per sec. used. For 21 of these frequencies a similar movement was obtained—that of extension of the ankle, flexion of the lateral 4 toes and adduction of the hallux—which may be designated as movement "A." Three different additive movements were obtained with the use of the 10 remaining cycles, flexion of the hallux (120, 180, 780, 840 c.p.s.), eversion at the ankle (360, 420, 480, 540, c.p.s.), and inversion (600 and 720 c.p.s.). These three additive movements, obtained with supraliminal stimuli, contained all the varieties of muscle contraction elicited with the liminal stimuli for some of these frequencies with two exceptions (i) extension of the toes, and (ii) abduction of the hallux. Therefore, if the repetitive stimulation of this point be considered as a whole, reversal of a part of the movement obtained with the liminal stimulus was elicited with the supraliminal stimulus, for the extension of the toes became flexion with the following frequencies:—660, 1200, 1260, 1320, 1380, and 1440 c.p.s. With 660 c.p.s. the abduction of the hallux obtained with the liminal stimulus became adduction with the supraliminal stimulus. The augmentations of movement "A" with either inversion or eversion at the ankle yielded by the supraliminal stimulation with all but one of the above cycles (360) were facilitations of the movements obtained by the liminal stimuli delivered by each of these frequencies. With 360 c.p.s. the supraliminal stimulus yielded a deviation of the movement produced by the liminal stimulus. Two of these frequencies refused to produce movement "A" with the strength of current which was sufficient to produce that movement with the remaining frequencies; for 1.0 mA. of the 10 c.p.s. and 1.3 mA. of the 5 c.p.s. were required.

Besides these characteristics of the response of a given cortical point to liminal and supraliminal stimuli of different frequencies, there was a measurable delay between the time when the given point was touched with the stigmatic electrode and the initiation of movement. For the supraliminal stimuli delivered to point C, this measurable delay (stop watch, graded in 0.01″) was found with certain of the higher cycles (1200 c.p.s., 1.4″; 1260 c.p.s., 0.9″; 1380 c.p.s., 1.0″) and with each of the 7 lowest (60 to 5) frequencies used. The longest delays occurred with 50 (1.7″), 20 (1.9″), 10 (1.1″) and with 5 (2.0″) c.p.s. For the liminal stimuli given the two points, D_2 and C, the movements elicited with certain of the higher frequencies (1140 to 1440 c.p.s.) were less delayed in their initiation (range 0.5″ to 1.2″, for pt. C and 1.2″ to 2″ for pt. D_2) than were those with the lower frequencies (5 to 60 c.p.s., range 1.0″ to 2.0″ for pt. C, and 1.5″ to 4.8″ for pt. D_2).

These delays were those recorded for the liminal intensity of the stimulating frequencies, capable of reproducing the movement initially elicited by a threshold stimulus of the 60 c.p.s. current applied to the chosen cortical point. In the search for the thresholds several intensities and their corresponding periods of delay were recorded with certain frequencies. For example, point D_2 (M's cortex) yielded some movement when stimulated with the following frequencies at the following intensities of current and their respective duration of applied stimulation as outlined in Table 1. Similar data were also obtained when point C (D's cortex) was stimulated with certain cycles (Table 2). Although the above data are obviously incomplete, they are sufficient to indicate that delay may be

a function not of the frequency only but also of the intensity of a given stimulating double vibration. Further, the height of the contraction elicited was reached more slowly when the chosen point was stimulated with the lower cycles (5 to 30 c.p.s.) than with any of the higher ones.

Table 1. Point D_2 (M's cortex)

c.p.s.	I in mA.	Duration in sec.
5	1.5	5.1
	1.75	4.6
10	1.75	5.2
	2.0	3.9
20	1.0	12.9
	1.25	3.3
30	1.5	11.6
	1.75	3.0
60	0.5	8.0
	0.65	1.5
	0.75	0.0
90	0.25	3.5
	0.30	1.6
	0.40	0.0
120	0.40	1.6
	0.50	1.6
	0.75	1.0
300	0.7	2.7
	0.75	2.6
420	0.65	3.0
	0.75	1.0
600	1.0	3.8
	1.25	0.0
960	1.25	6.0
	1.5	3.9

Table 2. Point C (D's cortex)

c.p.s.	I in mA.	Duration in sec.
5	0.6	2.0
	0.66	2.0
	1.0	1.8
10	0.6	1.9
	0.66	1.0
	1.0	1.1
20	0.53	2.0
	0.66	1.9
30	0.46	1.3
	0.66	0.9
40	0.4	1.5
	0.66	0.9
50	0.4	1.8
	0.66	1.7
60	0.2	2.1
	0.26	1.8
	0.36	2.0
	0.4	1.6
	0.66	0.5
240	0.2	1.8
	0.46	0.5
300	0.46	1.1
	0.66	0.3
480	0.36	3.0
	0.4	1.0
1200	0.4	0.9
	0.46	0.5
	0.66	1.4

The quality of the movement made by these muscles appeared to be a function of the cycle used. The movements elicited by stimulation either of point D_2 (*M*'s cortex) or of point C (*D*'s cortex) with frequencies of 20 or 30 c.p.s. were slow, deliberate and smooth; with 10 c.p.s., slow and jerky; and with 5 c.p.s., slow, tremulous and jerky but not decomposed into component parts. The movements elicited by frequencies greater than 90 c.p.s. were neither abrupt nor deliberate, nor were they tremulous. In the case of point D_2 on the cortex of *M*, jerky incompleted movements were elicited with the 3 highest cycles used (1260, 1380 and 1440); but in that of point C the movements were jerkily executed only at the highest frequency, 1440 c.p.s.

Discussion

Although analysis of movements elicited by electrical stimulation of the precentral gyrus can furnish only a first approximation to an understanding of the functional contribution of that cortex to the motor performance of the animal in question, nevertheless comparison of results of such studies in different animals has demonstrated that the resulting movements bear a direct relation to those which characterize the animal so stimulated (Hines and Boynton, 1940). This is particularly true if the current used be sinusoidal and the frequency, optimum or within its neighborhood. For the isolated movements and the co-innervations which were elicited could be correlated directly with those observed in the living animal at the time of the cortical exploration. Co-innervations include use patterns and their supporting movements, behavior patterns and patterns of progression or of posture. The first two can be elicited under deep ether anaesthesia. The last two can never be elicited in their entirety except under very light ether anaesthesia. The results of the stimulation of these three chimpanzee cortices can be analyzed in a similar way, except that throughout these explorations the anaesthesia was so deep that progression patterns were obtained only in fragments.

Contractions of isolated muscles were elicited. Certain of these isolated movements were obtained from each one of these cortices. The points from which these isolated movements were produced covered large cortical areas and suggested that cortici-fugal fibers are more numerous to certain motor nuclei within the segmental apparatus than to others. Thus the cortici-fugal fibers to the motor nuclei which supply the adductors of the first digits and the flexors of the lateral four could be considered as more numerous than those which supply the abductors of the first and the extensors of the remaining digits, while the projection fibers for such movements as opposition of the thumb, flexion or extension of the first digits, and flexion of the 2nd and of the 5th fingers would be relatively few. Similarly, isolated contractions of muscles were elicited by electrical stimulation of the face area, such as contraction of separate groups of fibers of the intrinsic muscles of the tongue and of those of the M. platysma or of the contralateral M. glossopharyngeus. It is evident then that it is possible to innervate separate motor nuclei within the spinal cord (pyramidal fibers apparently end among their component cells, Leyton and Sherrington, 1917) as well as functionally discrete portions of the nuclei of the N. facialis, or the N. hypoglossus, or the nucleus ambiguus of the N. vagus.

Certain combinations of the compound movements often recurred. Many of these co-innervations represented activation of the dorso-lateral or the ventro-lateral groups of nuclei within the spinal cord, innervating respectively the flexor sheet or the extensor sheet of muscles. Here, the cortical stimulation might be considered as activating spinal cord mechanisms rather than discrete nuclei and therefore as passing over the pyramidal terminals at the base of the dorsal horn (monkey, Schafer, 1884, 1899; monkey

and cat, Hoff, 1932). Thus, the occurrence of supination of the forearm with flexion of the elbow, and of pronation with extension of that joint, of protraction of the thigh with flexion of the knee, of adduction of the 1st digits with flexion of the lateral 4 or of abduction of the 1st with extension of the remaining 4, fell into this grouping.

Frequency of elicitation of certain movements as co-innervations and of others as isolated may be correlated with patterns of progression or of posture. When included as co-innervations with other movements, protraction of the thigh, flexion of the knee, retraction and abduction of the upper arm were more dominant than their respective antagonists. Certain other movements were always more frequently elicited than their antagonists, namely, retraction of the upper arm, external rotation of the thigh, pronation of the forearm and extension and inversion of the ankle. And additive extension of the digits was more frequent than additive flexion of the digits. The chimpanzee cannot extend its fingers completely, for the flexors are too short. In that ape's quadripedal progression the forelimb is supported upon the surface of the middle phalanx of the 2nd and the 3rd fingers; the wrist is extended; the forearm is pronated; the upper arm is more abducted than adducted, more retracted than protracted; the thigh is more protracted than retracted; the knee is only partially extended; the ankle is extended (*i.e.*, dorsi-flexed) and slightly inverted; the toes are loosely extended and the great toes abducted. In bipedal progression these characteristics of muscle use are emphasized. There is little fixation of the trunk; the thighs are abducted and slightly externally rotated; the knees are kept a little flexed; the ankles remain slightly inverted, so that progression proceeds as a side to side movement. With each protraction of the thigh the trunk flexes slightly. In brachiation partial extension of the fingers follows the sequence of movements initiated in more proximal muscles, retraction or abduction of the upper arm, and flexion of the elbow. In sitting the thighs are greatly abducted and externally rotated, the knees flexed, the ankle semi-extended and inverted; the upper arm is generally kept in semi-abduction, the elbow flexed and the forearm is in supination.

Besides these movements, co-innervations of flexor and extensor muscles were observed. These types of compound movements may be allocated to patterns of cortical selection. The use patterns of the distal muscles of the hand and foot require variegated co-innervations of supporting movements. Thus supination and pronation occurred with either extension or flexion of the wrist, or with either extension or flexion of the fingers; and flexion of the knee either with extension or flexion of the ankle. The use patterns themselves included those cooperative movements of the digits such as serial flexions, opposition of the 1st to one or more of the remaining in flexion and abduction of the 1st with extension of the 2nd.

A comparison of dominant isolated and compound movements with those outlined by Foerster for man (1936, pp. 48–49) clarifies the initial generalization, that the results of the stimulation of the precentral gyrus

bear a direct relation to the movements which characterize the normal usage of the animal in question. The chimpanzee cortex resembles that of man in the dominance of flexion of the digits and adduction of the first digit, of extension at the ankle and of flexion at the elbow, and of isolated retraction of the thigh and isolated extension of the knee; and differs from that of man first, in the dominance both of certain co-innervations (those of protraction at the thigh and those of flexion at the knee) and of retraction and abduction of the upper arm and pronation of the forearm, and second, in the infrequency of elicitation of opposition of the thumb and of isolated movements of individual fingers. No isolated movements of either the 3rd or the 4th fingers were obtained. They were also absent from Sherrington's series of 42 chimpanzees (total count of animals reported as used, 1901–1917)! Conversely, the results of electrical stimulation of the chimpanzee face area elicited isolated movements not as yet reported for man. Such movements were of the posterior, the middle or the anterior fibers of the M. longitudinalis superior of the tongue, the vertical fibers of the tongue, the contralateral M. glossopalatinus and parts of the M. platysma, and of the M. genioglossus (posterior part only).

The topographical projection of somatic musculature upon the precentral gyrus of these three chimpanzees (Fig. 4 and 5) varied in a few particulars from that given by Grünbaum and Sherrington (1901). The areas of the thumb and upper lip were contiguous; Grünbaum and Sherrington interpolated neck muscles between these two regions. However, examination of the maps given by Leyton and Sherrington (1917) show that movements of muscles of the neck were not invariably elicited. Stimulation of the face area of the foetal *Macaca mulatta* yielded movements of the muscles of the neck (M. sterno-cleido-mastoideus, for example) (Hines and Boynton, 1940) and of others attached to the shoulder girdle at a time in development before any movement of facial muscles could be produced, whereas later (older) such movements were obtained only occasionally when the ether was very light. Such might account for their sporadic occurrence in Leyton and Sherrington's experiments. That Krause (1912, p. 291) did not obtain them in man while Foerster (1936) and Penfield and Boldrey (1937) did, might be correlated with the conditions of their respective stimulations. Krause's patients were under a general anaesthesia.

Unlike Leyton and Sherrington the writers found different loci for antagonist movements of certain joints. Flexion of the fingers was ventral or anterior to extension; extension of the toes, ventral to flexion of the toes. Supination and pronation were generally placed dorsal to flexion or extension of the wrist. Flexion of the ankle (in *D*) was found ventral and caudal to extension of the ankle. And in this animal flexion of the hallux was ventral to the greater number of points giving adduction of that digit. These findings resemble in part Forester's for man. Penfield and Boldrey (1937) and Krause (1912) have found flexion and extension of the fingers separated in individual cortices.

The broad outlines of the projection of the remaining soma upon the precentral gyrus resembled that of Grünbaum and Sherrington. Movements of muscles of the trunk were found between those of the scapula below and the thigh above. However, in each of these animals, stimulation of a single point in this region produced not only movements of the chest wall but also changes in respiration—a finding unreported by other investigators. In this same general region not only were bilateral movements of the abdominal musculature obtained but also those of the thigh and knee. These latter movements resemble those obtained by Foerster with strong faradic stimulation. Similar movements were elicited in the young monkey (Hines and Boynton, 1940), and in the adult monkey after bilateral section of the medullary pyramids (Tower and Hines, 1935) from the anterior border of area 4. Here the excitation travelled by extrapyramidal projection fibers. Foerster, however, believed the movements he obtained in man travelled by ipsilateral pyramidal fibers.

Contraction of the Mm. constrictor ani et levator ani were found most ventral and anterior on the paracentral lobule. Movements of the thigh, the knee, the ankle and the toes were located there also in a manner which resembled more closely the findings of Foerster for man than those of Grünbaum and Sherrington for the chimpanzee.

Leyton and Sherrington reported visible movements of the vocal cords but no vocalization; Walker and Green (1938), vocalization "in only one experiment" by stimulation of the face area of the macaque. The localization of the two points from which a vocalization (V, Fig. 1) and a light whistle (W, Fig. 1) were elicited on the *M*'s precentral gyrus resembled those found for man by Penfield and Boldrey (1937) and by Penfield (1937). The point (see S in Fig. 1) from which salivation was elicited was located on the anterior crest of the central fissure. Salivation was produced by Walker and Green by stimulation of area 4 and area 6 (unspecified primate) and by Penfield and Boldrey (man) by that of the lower part of the postcentral gyrus (2 instances).

A few points on the postcentral gyrus responded without previous facilitation, therefore resembling the findings of Penfield and Boldrey (1937) for man rather than those of Sherrington for the chimpanzee. The writers have also been able to elicit movements which were neither synergic nor adversive not only from the postcentral gyrus (areas 3, 1, 2) but also from the parietal lobule of the macaque (adolescent and infant) without initial facilitation. This result may be correlated with the difference in the type of current used.

The stimulation of a few points within area 6, located on the caudal limb of the superior, middle and inferior frontal gyri elicited no adversive movements but rather movements which resembled Foerster's (1936, man) so-called synergies in contralateral musculature. These movements were protraction of the thigh and flexion at the knee with a single instance of additive extension of the ankle and flexion of the toes, retraction at the shoulder and flexion of the elbow, external rotation of the shoulder or of the upper

arm. While protraction of the thigh and flexion of the knee or the retraction of the shoulder and flexion of the elbow are partial synergies, they are also components in progression, to which extension of the ankle and the flexion of the toes are added. Similar movements have been observed by the writers to follow stimulation of homologous areas in young monkeys under light anaesthesia.

In the general exploration of the precentral gyrus with the 60 c.p.s. sine wave current, the amperage of the liminal stimuli was found to be lower in the face area than in either the arm or leg areas in all these animals. And the cytoarchitecture of the exposed surface of the face area is largely 6 (Campbell, 1903; Brodmann, 1912; Bucy, 1935; Walker and Green, 1938). Therefore unless the anterior limit of area 4 in these three precentral gyri be different from that outlined by these investigators, the lowest threshold was found in area 6.

On the other hand points located on the rostral crest of the inferior precentral fissure (area 6, Brodmann, 1912) had higher thresholds than any point located on the precentral gyrus itself. Again points on the anterior border of the leg and arm areas (no fissure present) had higher thresholds than those placed more rostrally. This sudden rise in threshold during the stimulation of a row of points probably indicated that the anterior boundary of the area giganto-pyramidalis was passed; for such a finding, later checked by histological studies, had repeatedly been found to be the case in previous studies (Boynton and Hines, 1933; Hines, 1937; Hines and Boynton, 1940) of this area in the brain of the *Macaca mulatta*.

All but a few low threshold points on the arm area yielded either isolated or primary movements of the fingers. No such similar distribution of low thresholds was found in the leg region, for movements of the thigh as well as the toes were found among them. Moreover, it was (Hines and Boynton, 1940) found that the lowest thresholds of points on the arm and leg areas of the young monkey gave, respectively, movements of the fingers and of the toes, when stimulated with the 60 cycle sine wave current.

The definite minimum in the curves produced by plotting in semilogarithmic coordinates the liminal peak amperage of the range of frequencies used to stimulate single points on the surface of the precentral gyrus occurred at 90 c.p.s. On either side of this optimum frequency (Coppée, 1936) the curve rose. Nevertheless, the range of lowest threshold frequencies was similar for the two curves presented in Fig. 6 (50 to 420 c.p.s.). Similar findings were reported as characteristic of homologous points similarly stimulated on the adult or year old macaque cortex (Hines and Boynton, 1940). Cooper and Denny-Brown (1927) recorded optically the responses of the M. brachialis anticus (*Macaca mulatta*) to cortical stimulation with a series of break shocks (35 to 90 p.s.) and with a rotating commutator (20 to 300 p.s.). They found that flexor muscles follow cortical stimulation up to 180 to 200 p.s. At higher rates the response became irregular and half rates were recorded. At lower rates of stimulation secondary waves were intro-

duced irregularly to make a total which varied from 180 to 200 ps. Rates lower than 8 p.s. rarely produced any response. But with 90 p.s. one primary response followed each stimulus and for each primary there was a secondary response establishing a regular double rhythm. The greatest regularity of response was to the rate of 90 p.s.; that is, the optimum frequency which we found for both the adult chimpanzee and for the adult macaque. It is just possible that this frequency is peculiar to these primates; for similar experiments on 2 other mammals the optimum frequency was different (Boynton and Hines, 1933; Straus and Hines, 1934).

Further, we noted that the delay between the time at which the electrode was applied to the cortical surface and the appearance of the contraction of the muscle was greater with the lower frequencies (60 to 5) than with the higher ones (660 to 1440). Cooper and Denny-Brown called this period of delay, the "summation period," and were able to measure it accurately. This "summation period" at times varied as much as 100 per cent with similar rates, in spite of care to avoid facilitation. Nevertheless as the rate per second decreased, the average "summation period" increased. There is also in our explorations, in spite of the unaccountable variables in such experiments as these, a relationship not only between the "summation period" and the frequency but also between the "summation period" and the strength of the stimulating current. For in general, the lower the intensity of current, the longer the "summation period" required to elicit movement; and below the optimum frequency the lower the frequency the longer the "summation period." With the highest frequencies used (1200 c.p.s. and above) the "summation period" increased. The rate of accumulation of excitation within the motor neurones then appears to be a function of the frequency as well as of the intensity of the stimulating current. But all frequencies used in these explorations produced movements. And the movements produced by stimulation of this cortical point with all of these frequencies showed no greater range of variability than those elicited by different intensities of a single frequency. What did vary was the quality of the movements elicited. The highest frequencies elicited jerky, incomplete movements, those of 30, 20 and 10 c.p.s. produced slow and deliberate movements, while to that of 5 c.p.s., the responding movements were not only slow but also tremulous. Apparently the central nervous system of the chimpanzee was able to accumulate all but the lowest frequency of excitation used; for tremors in somatic musculature are produced by rates of stimulation of peripheral nerves of 15 or less p.s. (Bronk, 1936). But the movements which resembled those seen in the unanaesthetized animal were elicited by the frequencies in the neighborhood of the optimum.

Summary

The precentral gyri of three adult chimpanzees were explored with the 60 c.p.s. sine wave current. The movements elicited were interpreted as activation (i) of discrete motor nuclei of the cranial and spinal nerves and

of parts of these nuclei; (ii) of groups of motor nuclei within the spinal cord which innervate extensor or flexor sheets of skeletal muscles; and (iii) of brain stem integration systems. Certain of the co-innervations suggest cortical selection of nuclear groups, such that use patterns were elicited.

The most frequently elicited movements of skeletal muscles were those of the digits, flexion of the lateral four and adduction of the first. Isolated movements of 2nd or 5th fingers were rare; those of the 3rd and 4th fingers did not occur. Different loci for antagonistic movements at the joints were obtained.

Vocalization, a light whistle, and salivation were produced in one chimpanzee. The postcentral gyrus responded without previous facilitation.

The liminal strength of the stimulating frequency for area 4 (arm and leg) was higher (0.22 to 2.0 mA.) than for the face area (largely area 6) (0.2 to 1.5 mA.).

A single point on two of these precentral gyri was stimulated with a range of double vibrations (5 to 1440 c.p.s.) of the sinusoidal current. 90 c.p.s. was the optimum frequency for each of these points. The frequencies eliciting movements which in their timing, sequence, and smoothness resembled characteristic of the unanaesthetized animal were those in the neighborhood of the optimum.

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1. BIRDSEY RENSHAW. Activity in the simplest spinal reflex pathways 373

2. F. H. LEWY and GEORGE D. GAMMON. Influence of sensory systems on spontaneous activity of cerebral cortex 388

3. D. NACHMANSOHN. Choline esterase in brain and spinal cord of sheep embryos 396

4. D. H. BARRON. Central course of "recurrent" sensory discharges .. 403

5. HOWARD J. CURTIS. Intercortical connections of corpus callosum as indicated by evoked potentials 407

6. HOWARD J. CURTIS. An analysis of cortical potentials mediated by the corpus callosum 414

7. KENDALL B. CORBIN and FRANK HARRISON. Function of mesencephalic root of fifth cranial nerve 423

8. WILLIAM D. SEYBOLD and ROBERT M. MOORE. Oculomotor nerve and reflex dilatation of pupil 436

9. MARION HINES. Movements elicited from precentral gyrus of adult chimpanzees by stimulation with sine wave currents 442